

Probing attentional biases

The presence and presentation of individual attentional biases in relation to salient stimuli

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Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen op
maandag 3 juni 2019
om 12.30 uur precies

door

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geboren op 30 december 1985
te Beneden-Leeuwen, West Maas en Waal

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Chapter 1

General Introduction

1.1 General

The aim of this thesis was to study attentional biases, specifically in relation to highly salient stimuli. The prominent role of pain-related stimuli should be seen in the light of the high saliency of these types of stimuli; pain demands attention, and therefore can force attentional shifts.

While this first chapter, chapter 1, the general introduction, establishes the terminology and current state of knowledge, the following chapters each cover a separate experiment, or certain, related, aspects of an experiment.

In chapter 2, attentional biases are investigated in a population of patients with CFS (Chronic Fatigue Syndrome), who are known for exhibiting attentional biases. To this end, the dot-probe task is refined to include movement-related and positive stimuli, next to the already included pain-related stimuli. Clinical measures are also employed, and psychological constructs are explored. The dot-probe task, together with clinical and otherwise validated questionnaires, is used to describe these patients in the light of attentional biases.

Chapters 3 and 4 concern a single experiment, where a dot-probe task employing highly salient pain-related word-based stimuli was used. These chapters deal with different and partially separate aspects of this experiment, and partially cover different fields, and have therefore been separated into two chapters and two articles, of which one article has been published. These chapters will now be introduced.

In chapter 3, attentional biases in the healthy population are investigated, using the dot-probe task to investigate potential relationships between reaction time-based measures and validated questionnaires, while taking the strength as well as the direction of an attentional bias into account. Psychological constructs such as fear of pain, hypervigilance, avoidance, and catastrophizing are central components in chapter 3, as is the dot-probe task itself.

Chapter 4 expands on the interindividual differences found in chapter 3, by analysing the ERPs (event-related potentials) as recorded during the experiment in chapter 3. These ERPs are the measures used to investigate the neural basis of attentional biases, as well as the possibility of the existence of interindividual differences. Again, the dot-probe task plays a leading role, but the interpretation of the Bias Indices, which played a major role in chapter 3, is relegated to a grouping variable, while the addition of EEG to the paradigm allows for objective measurements of brain activity in relation to the dot-probe.

In chapter 5, questionnaires and the EEG move to the foreground, in an experiment that measures personality traits regarding empathy and psychopathy in a social setting. During this experiment, painful electrical stimulation is used as opposed to pain-related words, and the resulting experiment concerns itself with delivering or receiving pain. Key outcomes are the neural responses in relation to questionnaire scores.

The concluding chapter, chapter 6, allows for a brief discussion of the results and their implications for current research and clinical practice, as well as directions for future research.

1.2 Attentional bias

There exist multiple cognitive processes that govern behaviour, such as memory, object recognition, and attention. While certain cognitive operations can be studied in relative isolation (such as object recognition), others are often studied in relation to other cognitive operations. For example, attentional processes allow us to focus and to select information relevant to the current task (Giambra & Quilter, 1988). Attention is thus involved in prioritising the limited processing capacity, by allocating cognitive resources selectively (Anderson, 2005).

Attention can be modulated by both external stimuli and internal phenomena (Treisman & Gelade, 1980). For example, a highly salient external stimulus, such as a painful pinprick, immediately redirects attention towards the relevant area on the body. From an information processing perspective, the term bottom-up is frequently used to describe the attention-drawing properties of these stimuli (Carrasco, 2011).

This is opposed to top-down attentional control; this redirects attention based on goals or pre-determined saliency (Broadbent & Broadbent, 1988; Carrasco, 2011). For example, if a participant is instructed to focus on a certain stimulus while ignoring others, then top-down attentional control is responsible for redirecting attention to that one specific stimulus while reducing the salience of the other stimuli. An external salient stimulus, which would normally attract attention, may be successfully ignored, allowing the participant to continue with its task (Posner, 1980).

Individual differences in processing pain-related stimuli (in high vigilant participants) have been shown to affect attentional processing of emotional cues (Dittmar, Baum, Schneider, & Lautenbacher, 2015; Eldar & Bar-Haim, 2010). Furthermore, top-down control has been suggested to play a large role in the processing of pain-related information, where it is theorised that bottom-up capture of attention is only possible if a stimulus exceeds a certain threshold, with top-down processes being able to selectively lower this threshold or amplify the information stream (Legrain et al., 2009).

There are certain limitations, though; top-down and bottom-up processes can be directly opposing or even generate conflict. Highly salient stimuli, such as pain, can essentially force an attentional shift, while the perceived importance of the task or situation may provide an equal force away from the highly salient stimulus (Nothdurft, 2002).

Pain, is a highly salient stimulus that (in general) signals harm or risk. As such, pain, as well as other salient stimuli, generally force an attentional shift, as such a shift may protect an individual from potential danger (Moore, Keogh, & Eccleston, 2012; Torta, Legrain, Mouraux, & Valentini, 2017).

The areas of the brain that are involved in the processing of and responding to such nociceptive stimuli are referred to as the pain matrix (Iannetti & Mouraux, 2010; Kupers & Kehlet, 2006). It refers to a complex neural network consisting of various areas dedicated to the perception and evaluation of pain and nociception, where the somatosensory cortices together with the anterior and posterior cingulate cortices play a central role, although the insula and the prefrontal cortex are also included (Price, 2000).

Recently, however, an attempt has been made to redefine or extend the pain matrix to salience matrix, as these same areas light up for other stimuli as well (Iannetti & Mouraux, 2010; Legrain, Iannetti, Plaghki, & Mouraux, 2011; Liberati et al., 2016). This specific cortical system reflects a system involved in detecting, orienting attention towards, and reacting to the occurrence of salient sensory events (Legrain et al., 2011). Nociception would be only one part of this system (Woo et al., 2017). Thus, the salience matrix is involved with both bottom-up processing, such as orienting toward a nociceptive stimulus, as with top-down processing, such as interpretation, response selection, and maintaining focused attention towards a specific type of salient stimuli.

During early attention, the orienting reflex is relevant, as it mainly deals with redirecting attention to unexpected or novel stimuli (Sokolov, Nezlina, Polyanskii, & Evtikhin, 2002). Any unexpected or novel stimulus potentially requires action, and therefore it will draw attention, allowing the individual to investigate and gather information, which is a prerequisite to be able to select an optimal (Williams et al., 2000).

As such, the orienting reflex can be seen as a primarily bottom-up response, while later processing relies more on top-down activity. The flexibility of this balance is shown after habituation of the system to a specific stimulus; after repeated exposure to the same stimulus, the orienting response tends to subside and disappear (Sokolov et al., 2002).

The balance between top-down and bottom-up processes can shift easily; injuries have been known to increase the weights of top-down contributors to pain processing, potentially driving bottom-up amplification through manipulation of salience of specific stimuli. This alteration of the salience levels can lead to far-reaching changes in behaviour (Vlaeyen & Crombez, 1999), which ensures exacerbation of the injury or re-injury is prevented. When the injury is resolved, the attentional systems should return to their previous state and the weights of the top-down contributors should be set back to normal.

In some cases, the changes are more persistent; individuals have been observed to exhibit atypical attentional biases, after a potential injury has been resolved (Asmundson, Carleton, & Ekong, 2005; Cockshell & Mathias, 2010; Haggman, Sharpe, Nicholas, & Refshauge, 2010). These attentional biases come in two forms; avoidance, which covers a shift in attention away from a stimulus that has a high saliency, and hypervigilance, which denotes the shift of attention towards the salient stimulus.

According to the vigilance-avoidance hypothesis, default processing of high-threat stimuli under normal circumstances results in an initial hypervigilance, followed by avoidance (Mogg, Bradley, Miles, & Dixon, 2004). This is considered to be an appropriate response; an injury requires initial hypervigilance to avoid further injury, but it should not impact normal functioning, hence avoidance follows. However, if hypervigilance or avoidance persists beyond the causative situation, it is considered non-optimal, and termed an attentional bias.

Recently, it has been suggested that pre-existing attentional biases may lead to an increased vulnerability to develop a chronic condition; for example, they have been suggested to play an important role in both the development as well as in the maintenance of chronic pain syndromes. Pre-existing attentional biases for pain-related information have been used as a predictor for later occurring post-operative pain (Lautenbacher et al., 2011; Lautenbacher et al., 2009). Other conditions, such as PTSD, have also been associated with a pre-existing attentional bias (Lin et al., 2015). Thus, attentional biases are not necessarily related to an injury or event, but rather act as predisposing factors in the risks for specific conditions, while the injury or event acts as a trigger.

Chronic fatigue Syndrome (CFS) is also characterized by atypical attentional processing, often culminating in pronounced attentional biases (Hou et al., 2014; Tiersky, Johnson, Lange, Natelson, & Deluca, 1997). While patients with CFS primarily show attentional biases towards health-related and threat-related information (Hou, Moss-Morris, Bradley, Peveler, & Mogg, 2008; Hou et al., 2014), there is some evidence that psychological constructs, including catastrophising, are altered as well (Cockshell & Mathias, 2010; Knoop, Prins, Moss-Morris, & Bleijenberg, 2010; Tiersky et al., 1997; Wiborg, Knoop, Frank, & Bleijenberg, 2012). Interestingly, personality traits seem to have a relation with CFS as well, where some personality traits, such as depressive traits, are more prominent or show an increased presence when compared with healthy controls (Nater et al., 2010).

1.3 Dot-probe

The first version of the dot-probe task was created by Halkiopoulos in 1981 to assess selective attention (Halkiopoulos, 1981). Figure 1.1 shows the different phases of a typical trial. This figure will be used to explain the relevant concepts in the following paragraphs.

A trial usually starts with a fixation cross (first pane of Figure 1.1). After a pre-defined period, two stimuli appear simultaneously (second pane), and the trial enters the word-phase. These stimulus pairs are either made up of two neutral words, which results in a neutral trial, or one neutral and one non-neutral word resulting in a non-neutral trial (note: the trial shown in the figure is a non-neutral trial). A stimulus pair remains visible for a pre-defined duration, after which it disappears. Presentation times are usually around 500ms, though presentation times can range from 100ms to 1250ms (Gray, Ambady, Lowenthal, & Deldin, 2004; Schmukle, 2005).

Directly after the disappearance of the stimuli pairs, a dot appears on a location previously occupied by one of the stimuli (right-most panes of Figure 1.1), which is used to probe the attentional effect of the previously shown stimulus pair. This phase is called the dot-phase. The participant is to respond to the location of the dot, as fast as possible. If the dot appears on the location previously occupied by the non-neutral word, the trial is termed congruent, and if the dot appears on the location previously occupied by the neutral word, it is termed incongruent (MacLeod, Mathews, & Tata, 1986).

This task is highly versatile; a wide range of visual stimuli, such as words (Haggman et al., 2010), pictures (Schoth & Liossi, 2010), and (Khatibi, Dehghani, Sharpe, Asmundson, & Pouretmad, 2009) have all been used in a wide range of different experiments.

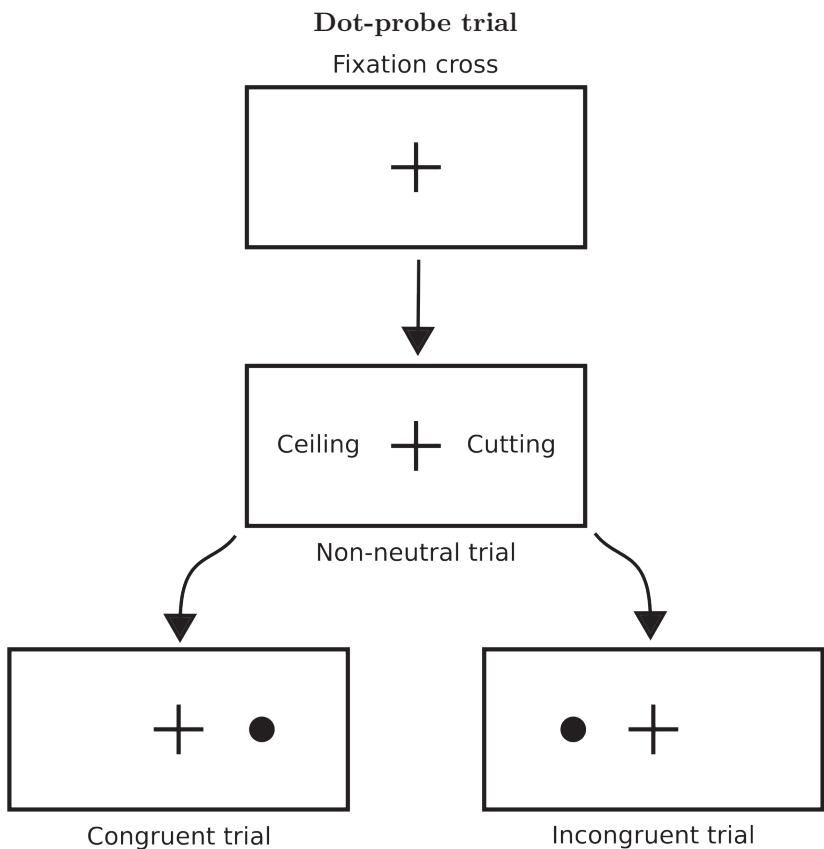


Figure 1.1: A typical dot-probe trial, in three steps. The upper pane shows the fixation cross, the middle pane shows the word-phase, and the lower panes show the dot-phase, with both possible locations of the dot and the required response by the participant.

Participants are expected to experience interference from the non-neutral word, which may speed up or slow down response times on specific combinations of locations of the non-neutral word and the subsequent dot. Figure 1.2 shows an example of reaction times for two theoretical participants, and their (attentional) bias-indices. This figure will be used to explain the relevant concepts in the following paragraphs.

Reaction times and bias indices

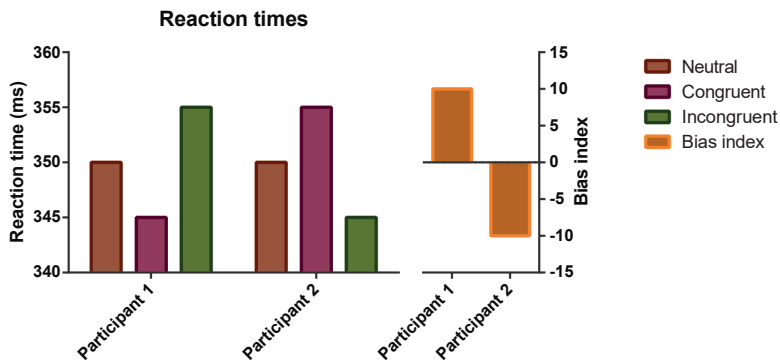


Figure 1.2: The left axis shows reaction times to three conditions, while the right pane shows the resulting bias indices. Note that the reaction time on neutral trials is shown, but does not contribute to the bias index. It should be noted that both participants are theoretical, and the absolute values are not representative of actual participants. Participant 1 is reacting faster on congruent trials when compared with incongruent trials, and therefore has a positive bias index. Participant 2 shows the opposite, and has a negative bias index

The example of participant 1 in Figure 1.2 shows a faster response on congruent trials (or: a lower reaction time) as compared to the reaction time on incongruent trials. This is commonly seen as hypervigilance, and is usually interpreted as being due to the perceived high salience of the stimulus (Asmundson, Carleton, & Ekong, 2005; Haggman et al., 2010; Roelofs, Peters, Fassaert, & Vlaeyen, 2005; Sharpe, Dear, & Schrieber, 2009); if a stimulus is highly salient, draws attention and hence a faster response, which can be measured as a lower reaction time.

The counterpart of hypervigilance is termed avoidance. The example of participant 1 in Figure 1.2 shows a slower response (or: a higher reaction time) on congruent trials, compared to incongruent trials. This delay is commonly interpreted as being the result of an initial attentional shift away from the non-neutral word, which then introduces a delay if the dot appears on the location of the non-neutral word. This avoiding is synonymous with attentional avoidance.

The average reaction times on the congruent and incongruent conditions can be used to compute the attentional Bias Index (BI), which can be seen in the right axes of Figure 1.2. The BI is a commonly used parameter which describes the direction and strength of an attentional bias as measured with specific (Cosentino, Werning, & Reuter, 2011; Richter, Eck, Straube, Miltner, & Weiss, 2010). As the BI is calculated from the difference between the congruent and the incongruent reaction times, its sign can be related to hypervigilance (positive) or avoidance (negative). The value of the BI denotes the strength of the bias; a higher value, irrespective of the sign, is representative of a stronger bias.

Most implementations of the dot-probe task are visual, using words or images. Words are commonly seen as a valid substitute for the actual salient stimuli, such as actual painful stimuli. It has been reported that there is indeed a relation between pain sensitivity and word associations for pain-related words (Cong, Kalyakin, Ristaniemi, & Lyytinen, 2011). Another study reported that brain activation, as measured with EEG, is similar between the conditions of experiencing painful stimulation and processing pain-related words (Richter et al., 2010). The authors argue that this cannot be explained by the valence of, or arousal evoked by, the words. Moreover, utilizing words is usually preferred to exposing participants to actual painful stimuli, due to primarily ethical reasons.

Furthermore, the usage of words allows for a wide range in stimulus content, including, but not limited to, health-threatening information (Hou et al., 2008), pain-related information (Van Ryckeghem, Crombez, Van Hulle, & Van Damme, 2012), general negative information (Blaut, Paulewicz, Szastok, Prochwicz, & Koster, 2013). Aspects such as ambiguity can also be employed (Schrooten, Vancleef, & Vlaeyen, 2015). Manipulating the content of the stimuli (words, or otherwise) therefore allows the task to be used in a broad spectrum of conditions or situations. In some studies, separate sets of words covering different categories of information are combined in a single experiment to study multiple attentional BIs, such as a separate attentional BI for affective and sensory pain-related words (Keogh & Cochrane, 2002).

Presentation time can also be manipulated, which has shown attentional biases to be transient, suggesting a gradient of bottom-up towards top-down attentional processing (Bögels & Mansell, 2004). Short presentation times are more likely to reflect the initial orienting (Bradley, Mogg, & Millar, 2000), while longer presentation times allow for other aspects, such as evaluation and rumination, to affect response delays (Donaldson, Lam, & Mathews, 2007). This supports the idea that both bottom-up and top down processes together result in attentional biases.

1.4 The electro-encephalogram (EEG)

There are several methods to make the activity of the brain visible, each with their own strengths and drawbacks (Fish & Spencer, 1995). Functional magnetic resonance imaging (fMRI), for example, excels in spatial localization but has a relatively low temporal resolution. The electroencephalogram (EEG) however has a high temporal resolution yet has a very low spatial resolution. While fMRI measures brain activity indirectly, the EEG is a non-invasive technique that records the actual electrical activity generated by large assemblies of neurons.

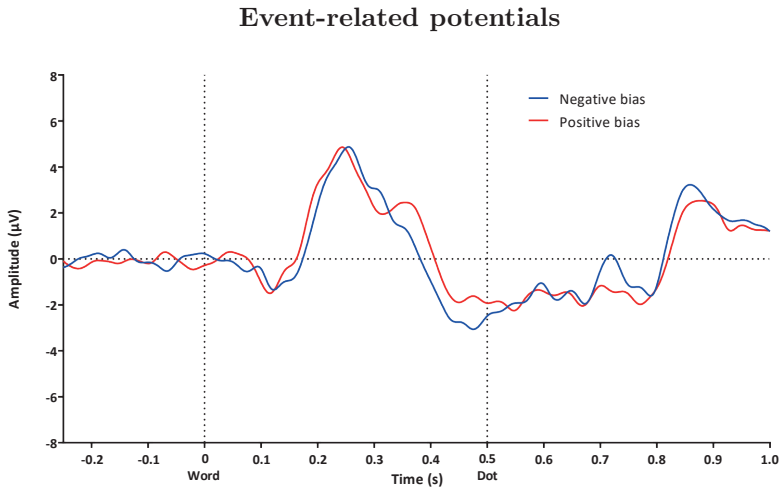


Figure 1.3: Two ERPs are shown in two colours, allowing for easy comparison. These two ERPs are generated based on data used in chapter 4. The appearance of the words and the appearance of the dot are events, and labeled on the time-axis. Note that the vertical axis, which shows the amplitude in millivolts, is plotted with negative voltages downward. Two ERPs are shown in two colours, allowing for comparison.

One of the most versatile and frequently employed methods in cognitive EEG research is the event-related potential (ERP) methodology (Luck, 2005a; Luck, 2005b; Luck, 2005c). To ensure comparability and reproducibility, several guidelines have been created (Carrasco, 2011; Hickey, van Zoest, & Theeuwes, 2010; Mayer, Dorflinger, Rao, & Seidenberg, 2004; Posner, 1980).

In short, to obtain an ERP, a stimulus (such as a light, image, symbol, sound, or a word) is presented multiple times, and the resulting EEG traces are averaged resulting in a single averaged reaction. Activity that is time-locked to the stimulus will remain visible in the average, while activity that is not time-locked to the stimulus will be cancelled out. This method relies on the relative consistency in stimulus-processing speed to make these reactions visible.

The resulting ERP (see Figure 1.3) shows the progression of the averaged neural activity over time. In these averaged ERP tracings, peaks and troughs are visible, which are commonly seen as the ERPs components. Most components appear across paradigms, and are therefore often used as representative of a specific aspect of information processing, such as early perception, attention allocation, stimulus evaluation, or response selection.

The labelling of ERP components is generally based on polarity and temporal order. Most components are referred to by a letter indicating polarity (N for negative, P for positive), followed by the latency in milliseconds; a P50 therefore is a positive deflection at 50ms (Luck, 2005a).

It is commonly thought that earlier components (i.e. occurring within the first 50ms) are determined by the physical stimulus characteristics and are therefore classified as the exogenous-components. Later occurring components are thought to represent cortical processing stages, which are less determined by the physical features of the stimulus, but determined by the cognitive aspects of stimulus processing and are therefore classified as endogenous components (Brockhaus-Dumke et al., 2008).

One of the earlier components that has been intensively investigated using ERPs is the P50 (positive deflection at 50ms), which is usually which is usually seen as representative of filtering (Brockhaus-Dumke et al., 2008). As the ERP progresses, more components can be identified; the N100 (negative deflection at 100ms), which has been associated with stimulus predictability (Butler, 1968; Lightfoot, 2016), but also with top-down attentional processes (Brockhaus-Dumke et al., 2008; Furutsuka, 1989; Nash & Williams, n.d.).

The later P300 complex is understood to reflect higher-order cognitive functions. Several sub-components can be distinguished, for example the P3a, which is also termed the novelty P3, as it reacts to the novelty of a stimulus, and is associated with the engagement of attention (Polich, 2003). The P3b represents a later cognitive step, and has been associated with cognitive load (Donchin & Coles, 1988; Kok, 2001), response selection and preparation (Verleger, Jaśkowski, & Wascher, 2005), and even event categorisation (Kok, 2001) and memory formation (Polich, 2007).

A comparison between ERPs in different conditions can show changes in both the earlier endogenous components that have been associated with bottom-up attentional processes (such as the P50 and N1 component), and the later occurring endogenous components that are known to be affected by top-down processes (such as the N2 and P3 components).

EEG has been previously employed in the study of attentional biases, where it allows for a fine-grained approach towards the temporal characteristics of attention (Bar-Haim, Lamy, & Glickman, 2005).

A recent study using faces to elicit attentional biases demonstrated the early activation of the fusiform gyrus to be related with hypervigilance, while a later occurring activation of the fusiform gyrus to be associated with avoidance (Mueller et al., 2011).

Finally, attentional training has been shown to result in changes in the ERP, suggestive of neural plasticity, which can be taken to indicate that attentional training modulates top-down processes of attentional (Legrain et al., 2009).

1.5 Assessing interindividual differences in attitudes towards pain and pain-related concepts

EEG is a good choice for making brain activity visible, and the dot-probe is appropriate for revealing attentional biases. However, both measure objective phenomena. Psychological constructs and subjective aspects of processing are often measured through subjective means, by self-report measures such as questionnaires. Most questionnaires used in a clinical or academic setting focus on specific constructs, allowing for easy selection and collection of questionnaires for most purposes. The questionnaire was first employed by the Statistical Society of London in 1838 (Heywood, 1838).

In examining attentional biases, it is evident that measures of vigilance are crucially involved. To date, most studies have incorporated the Pain Vigilance and Awareness Questionnaire (PVAQ), a measure of generalized attention directed towards pain. It was created to assess awareness, vigilance, preoccupation, and observation of pain and is expected to be most suited to detect differing attentional biases, specifically the increased vigilance (McWilliams & Asmundson, 2001).

The PVAQ is also suited for use in a non-clinical sample, and shows good internal consistency as well as associations with relevant pain-related measures (Roelofs et al. 2003). Specifically, the PVAQ has been shown to relate to pain perception and patient-controlled analgesia, and has shown to possess predictive power (Lautenbacher et al., 2011). The PVAQ has even demonstrated links with several ERP components, which can be taken to suggest it is indeed touching upon underlying neural phenomena (Dittmar, Krehl, & Lautenbacher, 2011).

The processing of pain and evaluation of pain-related stimuli can be quantified with the Pain Anxiety Symptoms Scale (PASS) (Osman, Barrios, Osman, Schneekloth, & Troutman, 1994). The PASS has shown links with ERP components, similar as the PVAQ (Dittmar et al., 2011), and has been found to make significant and unique contributions to the prediction of both disability and interference with activities of daily living due to pain (McCracken, Zayfert, & Gross, 1992).

Confirmatory factor analysis has shown that the total PASS score can be used, but has also indicated support for the PASS as a four-factor model (Osman et al. 1994). As such, the PASS can be separated into several subscales estimating specific components of pain-related constructs, such as cognitions, escape or avoidance-related tendencies, fear, and physiological aspects. The fear subscale is specific for Fear of Pain (FoP), which is commonly seen as a major factor in the processing and evaluation of pain-related stimuli (Vlaeyen, Crombez, & Linton, 2016).

However, there exists a specialized questionnaire for FoP: the Tampa Scale for Kinesiophobia (TSK), which is designed to measure fear of movement and fear of (re)injury during movements and can be separated into two factors: Somatic Focus and Activity (McCracken et al., 1992; Roelofs et al., 2007).

Interactions between attentional biases and scores on the TKS have been shown many times, suggesting that the factors measured by the TKS do indeed have potential value (Asmundson, Vlaeyen, & Crombez, 2004; Pincus, Smeets, Simmonds, & Sullivan, 2010; Roelofs et al., 2005; Vlaeyen & Linton, 2000; Vlaeyen et al., 2016).

Catastrophising is another construct that seems to play a sizable role in the processing of highly salient stimuli. Regarding pain, the Pain Catastrophizing Scale (PCS) has been developed, which measures elements of catastrophizing behaviour (Sullivan, Bishop, & Pivik, 1995). It can be separated into three subscales: rumination, magnification, and helplessness, which are all constructs associated with catastrophizing. This questionnaire has been shown to be robust and reliable (Van Damme, Crombez, Bijttebier, Goubert, & Van Houdenhove, 2002).

Catastrophising has been associated with pain processing, especially in clinically relevant samples, such as chronic pain patients, where it appears to mediate the positive pain outcomes (i.e.; reduction of pain) of treatments incorporating exercise (Goodin et al., 2009).

Catastrophising has also been implicated in the transition from post-operative pain to chronic pain (Keogh & Cochrane, 2002), and as such has been employed as a predictor of chronic (Grosen, Vase, Pilegaard, Pfeiffer-Jensen, & Drewes, 2014).

Interestingly, positive traits and emotions, as well as psychological resilience, have been connected to catastrophising as mediators or moderators (Ong, Zautra, & Reid, 2010; Poppe et al., 2011; Pulvers & Hood, 2013).

Attentional biases have been shown to exist in patients with a major depressive disorder. One notable study showed this using an eye-tracking task, where patients showed heightened allocation of attention to sad faces, and less attention to happy faces, compared with controls (Trapp, Kalzendorf, Baum, Hajak, & Lautenbacher, 2018). Other studies show similar effects, but included attentional biases towards pain and several emotional stimuli. Based on these outcomes the authors concluded that patients with pronounced depression show an increased early attentional engagement towards emotional salient stimuli, independent from valence (Goubert, Crombez, Van Damme, et al., 2004; Roelofs et al., 2007).

Measuring sub-clinical levels of depression, in relation to attentional biases, would therefore be helpful, and the Beck Depression Inventory (BDI) allows this. While originally designed in 1961 as a clinical tool to estimate the severity of a depressive disorder (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), its robustness makes it capable in measuring sub-clinical levels in the normal, healthy population (Beck, Steer, & Carbin, 1988; Strunk & Lane, 2016).

Depression has been shown to have a relationship with pain thresholds and pain tolerance, where an increase in the score on the BDI is related with lower thresholds and lower tolerance (Duque & Vázquez, 2015; Meeus, Nijs, Van Mol, Truijen, & De Meirleir, 2012).

Subjective amplification of sensory input also seems to play a role; it is a complex phenomenon implicated in the risk, development, and possibly in the maintenance of many disorders (Duddu, Isaac, & Chaturvedi, 2006), including chronic fatigue (Geisser et al., 2008) and chronic pain (Kosturek, Gregory, Sousou, & Trief, 1998). It has also demonstrated links with anxiety and depression (Duddu et al., 2006; Yavuz, Aydinlar, Dikmen, & Incesu, 2013), suggesting it may be a major component of cognitions and beliefs related to sensory processing, including pain. The Somatosensory Amplification Scale (SAS) is the questionnaire that can measure subjective amplification of sensory input, and does so by asking questions such as “Sudden loud noises really bother me” (Duddu et al., 2006).

Although several constructs refer to aspects of an individual’s state, some may be representative of more deeply embedded personality trait. Moreover, several personality traits, including neuroticism and extraversion, have been linked to experimental pain sensitivity, as well as to chronic pain (Poppe et al., 2011). As such, personality traits may need to be investigated as well.

The Eysenck Personality Questionnaire (EPQ) measures a participant’s personality using separate scales: social desirability, extraversion, neuroticism and psychoticism. These personality traits have been associated with low acceptance of pain and catastrophising as well, which would mean that personality traits potentially impact recovery and rehabilitation (Bögels & Mansell, 2004). Interestingly, one personality trait has been directly associated with a higher tolerance for painful stimulation (Miller, Rausher, Hyatt, Maples, & Zeichner, 2014), as well as a lower neural response to pain in others (Gray et al., 2004; Seara-Cardoso, Viding, Lickley, & Sebastian, 2015); psychopathic traits. These traits exist in sub-clinical form in the general population (Coid, Yang, Ullrich, Roberts, & Hare, 2009; Levenson, Kiehl, & Fitzpatrick, 1995; Lilienfeld, Latzman, Watts, Smith, & Dutton, 2014).

1.6 The current thesis

Patients suffering from CFS have been known to show pronounced attentional biases, as well as chronic pain. In chapter 2, this population was investigated, with specific focus on the degree of fatigue, due to the high disease load. The usage of multiple stimulus types relevant to different aspects of CFS is expected to shed additional light on the underlying relations, and we expect biases regarding pain-related and movement-related information to have clear relations with the established constructs.

The existence and presentation of attentional biases remains an issue. One notable meta-analysis showed strong disagreement in literature regarding attentional biases, where similar studies report opposing results (Bögels & Mansell, 2004). Since this likely impacts all aspects of research into attentional biases, this is an extremely relevant issue. As such, in chapter 3, we performed an exploratory study into attentional biases. Specific focus is placed on a potential non-linear presentation, which may explain the variation in results. We expected that the direction and magnitude of attentional biases are separate measures, and, while taking interindividual differences into account, that these have separate relationships with specific constructs, such as Fear of Pain and Catastrophising.

The neural basis of attentional biases is insufficiently established, as is evident from the relatively small number of studies including neural measures. In chapter 4 we aimed to further establish the neural basis of attentional biases. We expect to find clear and meaningful neural differences between subgroups.

Moreover, the cause-and-effect discussion has been largely ignored; it is currently unknown if attentional biases pre-exist disorders, or if they follow from disorders. In chapter 4, we also aimed to provide evidence for potential trait differences, which would suggest attentional biases are independent of a slower or faster response to specific stimuli.

Highly salient stimuli are processed differently based on interindividual differences, while the research into this has been mainly limited to positive information and positive traits. Other personality traits have only rarely been included, while there is evidence of altered processing of highly salient (painful) stimuli in certain subgroups of the general population. As such, in chapter 5, empathy and psychopathic traits were taken as potential predictors of neural differences in the processing of highly-salient stimuli between individuals. We also expected to find neural differences related to psychopathic and empathic traits.

Chapter 2

Attentional biases in chronic fatigue syndrome

Support for a fear-avoidance model?

This chapter is based on:

van Heck, C. H., Knoop, J., Rombout, L., van Rijn, C., & Oosterman, J. (2019). Attentional biases in chronic fatigue syndrome; support for a fear-avoidance model? (in preparation)

Abstract

Chronic Fatigue Syndrome (CFS) is a syndrome marked by severe, disabling fatigue, which does not improve with rest. Patients commonly present with cognitive symptoms, as well as chronic pain. No current model explains how CFS is triggered or maintained. However, for chronic pain multiple studies have supported the fear-avoidance model, which connects constructs such as fear of pain, catastrophising, and avoidance into a positive feedback loop, which then maintains or worsens the chronic condition. In this study, we investigate the fit of the fear-avoidance model of pain in CFS.

Forty-four patients and sixty-seven controls were included. All participants performed a dot-probe experiment using pain-related, movement-related, and positive words, resulting in Bias Indices (BI) for each of the three word-categories. Questionnaires were employed to quantify psychological constructs.

Patients showed higher fatigue, increased somatic focus, and more pronounced somatosensory amplification, as well as avoidance of movement-related information. Patients showed a trend suggestive of hypervigilance regarding pain-related information, while controls showed a trend suggestive of avoidance.

No association between any of the psychological constructs (e.g., fear of movement, fatigue) and the attentional biases for pain or movement-related information was found. The construct helplessness showed a positive correlation with the positive BI in both groups, while constructs regarding activity and avoidance of activity showed positive correlations with the positive BI in the patients only.

This study provides support for the utility of the fear-avoidance model of pain in explaining CFS-symptoms. Secondly, we suggest that (the processing of) positive information may also play a role in CFS. Finally, as the effects regarding the biases are relatively small, we suggest future studies to enlarge sample sizes and include other factors.

2.1 Introduction

Chronic Fatigue Syndrome (CFS) is a syndrome marked by severe, disabling fatigue, which is medically unexplained. This fatigue does not improve with rest, and negatively affects daily functioning, as well as quality of life (Anderson & Ferrans, 1997; Prins, van der Meer, & Bleijenberg, 2006). Patients with CFS commonly present with a range of symptoms, such as unrefreshing sleep, concentration and memory problems, post-exertional malaise, and/or pain, which varies in intensity and presentation across individuals (Evengård, Schacterle, & Komaroff, 1999), but is highly prevalent nonetheless; some studies suggest the vast majority of CFS patients experiences pain (Johnston, Brenu, Staines, & Marshall-Gradisnik, 2013; Vincent et al., 2012). This pain, which is often chronic in nature, can be associated with several psychological constructs, such as kinesiophobia and catastrophising (Meeus et al., 2012). Kinesiophobia has also been linked to fibromyalgia as well as other chronic pain syndromes (Goubert, Crombez, Van Damme, et al., 2004).

A subgroup of patients with CFS also show altered cognitive processing, which may include impaired processing speed (Anderson & Ferrans, 1997; Cockshell & Mathias, 2010; LaManca et al., 1998) or attentional control functions (Glass, 2006). Interestingly, a discrepancy is often found between the degree of subjective complaints and the measured, objective, cognitive impairments (Goedendorp, van der Werf, Bleijenberg, Tummers, & Knoop, 2013; Tiersky et al., 1997).

Several cognitive behavioural models have been proposed to explain how CFS can be triggered and which factors are involved in the maintenance of CFS symptoms. These models are typically based on the notion that attentional processes play an important role in the risk for developing the syndrome (Hou et al., 2014) as well as symptom maintenance (Wiborg et al., 2012). Specific relationships, such as the feedback loop between avoidance of physical activity and deconditioning (such as a loss of capacity for activity) (Wessely, David, Butler, & Chalder, 1989), have, over time, been integrated to form complex models (Hou et al., 2008; Vercoulen et al., 1994; Vercoulen et al., 1998; Wiborg et al., 2012). Most models focus on fatigue or pain as central features of CFS and do not specify their interrelationship.

It has been argued that cognitive processes themselves play a central role in the maintenance of symptoms (Knoop et al., 2010). These cognitive processes usually concern perceptions and beliefs, which in turn may be driven or supported by attentional processes in the form of attentional biases. Attentional biases have indeed been suggested to play a role in the development or maintenance of CFS (Cockshell & Mathias, 2010), and attentional biases have been reported to exist in these patients in relation to several stimuli types, such as pain-related, movement-related, and disease-related information (Hou et al., 2014; Hughes, Hirsch, Chalder, & Moss-Morris, 2016; Nijs et al., 2013).

Note that in this chapter, we focus on the fear-avoidance model, which attempts to integrate the aforementioned cognitive processes with specific behaviours, and its relationship with attentional biases. However, instead of focusing on one specific stimulus type, we will employ salient word-based stimuli. Pain can be seen as a highly salient stimulus (Legrain et al., 2011), and due to the nature of the complaints, movement-related stimuli are employed as an additional measure.

It has been shown that fear of movement and avoidance behaviour toward physical activity, as conceptualized in the fear-avoidance model in relation to pain, are prevalent in CFS (Nijs et al., 2013). Within this model, participants with a high fear of pain or (re-)injury are expected to show avoidance in relation to physical activity, which can lead to maintenance or even exacerbation of fear and physical limitations (Bortz, 1984). This avoidance is the result of a positive feedback loop where individuals catastrophize after experiencing pain.

This, according to the model, may lead to hypervigilance towards the pain or the related cues, as well as avoidance of possible sources of pain, such as movement (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012). Hypervigilance can also be directly linked to greater pain severity, and has been used as a predictor for postoperative pain (Herbert et al., 2013; Lautenbacher et al., 2009).

Catastrophizing is a crucial part of the fear-avoidance model and can be seen as a process opposing adequate 'coping'. Therefore, it is not surprising that catastrophizing and coping behaviour have been associated both with chronic pain syndromes and with CFS (Goubert, Crombez, & Van Damme, 2004; Meeus et al., 2012). Furthermore, catastrophizing as well as avoidance have been associated with increased symptom severity and poorer recovery after surgery or injury, lower general health, and lower quality of life (Asmundson, Norton, & Norton, 1999; Goodin et al., 2009), and both have been suggested as predictors for chronic pain and surgery recovery (Cook, Brawer, & Vowles, 2006; Lautenbacher et al., 2011; Pulvers & Hood, 2013). Furthermore, the role of catastrophizing in pain processing and subjective pain ratings has been repeatedly demonstrated (Pulvers & Hood, 2013; Sullivan, Rodgers, & Kirsch, 2001), and has been related to attentional bias (Sullivan et al., 2001).

CFS patients have been known to show significantly less physical activity than healthy controls, in line with this avoidance model (Nijs et al., 2013). Increased avoidance behaviour of movement in CFS has been associated with generally poorer patient outcomes as well as with higher subjective pain ratings and increased vigilance towards pain (Andrews, Strong, & Meredith, 2012; Nijs et al., 2013; Vercoulen et al., 1994).

The extent to which attentional biases for pain and movement-related information are present in CFS remains unclear. One important factor may be that most studies are limited in the employed stimuli; most studies have examined attentional biases using information that relates negatively to health (such as health-threatening word-based stimuli; ‘coffin’, ‘paralyzed’). Specifically, it was found that a high level of anxiety sensitivity could be related to a greater attentional bias for threat (Lees, Mogg, & Bradley, 2005). Similar results have been reported in other studies (Hou et al., 2014), and one study has suggested a similar bias may exist towards illness-related information (Hughes et al., 2016). Although these stimuli can be related to the heightened focus on somatic symptoms seen in patients with CFS (Moss-Morris & Petrie, 2003), they might not represent the full extent of the attentional biases present in CFS.

Since CFS is frequently accompanied by (chronic) pain, and it may share at least some cognitive factors with pain processing, the fear-avoidance model of pain has also been employed to explain other aspects of CFS (Meeus & Nijs, 2007; Meeus et al., 2012; Nijs et al., 2013). Based on this model, an attentional bias in relation to pain-related stimuli in CFS can be expected, or a potential attentional bias in relation to movement-related stimuli or movement itself.

As evidenced by the associated neural correlates, both pain (Chen, Dworkin, Haug, & Gehrig, 1989; Treede, Kenshalo, Gracely, & Jones, 1999) and fatigue (Cheng & Hsu, 2011; Trejo et al., 2007; van Duinen, Renken, Maurits, & Zijdwind, 2007) are central phenomena. While pain as a central and neural phenomenon is widely-accepted and frequently investigated, CFS has received less attention, although significant differences in neural activity (Billiot, Budzynski, & Andrasik, 1997; Duffy, McAnulty, McCreary, Cuchural, & Komaroff, 2011; Flor-Henry, Lind, & Koles, 2010) and neural structure (de Lange et al., 2004) have been found.

The extent to which a bias for pain and movement-related information is present in CFS is to date unclear. The goal of the present study is to fill this gap by examining the possible presence and direction (i.e., hypervigilance versus avoidance behaviour) of an attentional bias for pain and movement-related information in patients with CFS.

More specifically, we hypothesize:

1. That patients with CFS will show an increased bias when compared with healthy controls, for both pain and movement-related information. In line with the fear-avoidance model, we expect that patients will primarily show hypervigilance for pain-related information, as well as avoidance of movement-related information, in contrast with the controls.
2. We expect that anxiety, pain catastrophizing, the level of fatigue and pain severity are associated with the strength of attentional biases for pain and movement-associated stimuli.

2.2 Materials and methods

2.2.1 Participants

A total of 25 patients were included at a tertiary CFS treatment centre at the Radboud University Medical Center in Nijmegen, the Netherlands. A second group of 19 patients was recruited through the Dutch CFS/ME patient organisation (the ME/CVS Stichting), resulting in a total population of 44 patients suffering from CFS. Patients were only included if they were diagnosed with CFS according to the U.S. Centre for Disease control (CDC) criteria (Fukuda et al., 1994). Additionally, patients were excluded if they were not severely fatigued or experienced limitations in their functioning.

Healthy controls were recruited via the participating patients from their own social network ($N = 14$), and included family members, partners, or friends. Additional controls ($N = 53$) were recruited through advertisements or social media, resulting in a total of 67 controls.

Both healthy controls and the patients were subject to standard exclusion criteria, such as dyslexia, diabetes, cardiovascular problems, or substance abuse (now and in the past). Healthy controls were also excluded if they reported depression now or in the past, were suffering from a chronic pain syndrome, were seeing a psychologist, or if they were using psychoactive medication for any reason or yielded scores that exceeded clinical thresholds. Exclusions during the data-collection phase are noted under ‘results’.

This study was approved by the Ethic Committee Social Sciences (registered under *ECSW2016-2208-414*) of the Radboud University in Nijmegen and was performed in accordance with the requirements of the Declaration of Helsinki. The Medical Research Ethics Committee of Radboud University Medical Center (CMO Regio Arnhem-Nijmegen) waived formal evaluation of the study (which is registered under *2015-2243*). All participants signed a written informed consent.

2.2.2 Self-report measures

In order to examine the properties of the groups and subgroups, several questionnaires were included:

1. A general background questionnaire (age, sex, educational level, etc.), which also functioned to confirm symptoms in accordance with CDC criteria for CFS.
2. The Checklist Individual Strength (CIS20-R), a questionnaire which is specifically designed to assess several dimension of fatigue (Worm-Smeitink et al., 2017). This questionnaire obtains scores using a 7-point Likert scale, and can be subdivided into four subscales, which describe the separate dimensions of CFS: *Concentration*, *Motivation*, *Physical activity*, and *Fatigue Severity*. The Fatigue Severity subscale is employed as a clinical measure with a clinical threshold of 35 points, meaning that patients who score below (not showing clinically relevant fatigue), and controls who score above (showing clinically relevant fatigue) this threshold would need be excluded.

3. The Tampa Kinesiophobia Scale (TKS), which measures fear of movement and fear of (re)injury during movements, and can be separated into two factors: *Somatic Focus* and *Activity Avoidance* (Goubert, Crombez, Van Damme, et al., 2004).
4. The Sickness Impact Profile (SIP), which is a measure of health status based on behaviour (Bergner, Bobbitt, Carter, & Gilson, 1981). This questionnaire can be used to assess overall functional impairment in eight different areas. This questionnaire was administered to the patients only. Two versions of the SIP were employed; the SIP68 and the SIP8.
5. The Pain Catastrophizing Scale (PCS), which measures elements of catastrophizing behaviour. It can be separated into three subscales: *rumination*, *magnification*, and *helplessness*, which are all constructs associated with catastrophizing (Sullivan et al., 1995).
6. The Somatosensory Amplification Scale (SAS), which is a measure of subjective amplification of sensory input. Somatosensory amplification is a complex phenomenon implicated in the risk, development, and possibly maintenance of many disorders, including chronic fatigue (Duddu et al., 2006; Geisser et al., 2008). It does so by asking questions regarding potential subjective amplification, such as “Sudden loud noises really bother me”.

2.2.3 Procedure

All participants were exposed to the same procedure. Before starting the experiment, participants were explained that attention was the focus of this study, and that attentional effects would be measured through an experiment on a computer. It was also explained that the instruction was standardised, and in an effort to limit interference, questions not pertaining to their required actions during the experiment needed to be held until after completion of the questionnaires and tasks.

It should be noted that the patients recruited via the CFS treatment centre performed the tasks in the hospital, during regular visits, while patients recruited via the foundation for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis performed the tasks at home, under supervision. They performed the same tasks within the same protocol.

Attentional biases are commonly investigated using the dot-probe paradigm, a paradigm specifically designed to shed light on attentional biases (Halkiopoulos, 1981; MacLeod et al., 1986). Using this method, one can determine the direction (towards, or away from, non-neutral stimuli) and strength of an attentional bias. The dot-probe experiment, as used here, was based on versions employed in previous research (van Heck, Oosterman, de Kleijn, Jongsma, & van Rijn, 2017).

A total of 75 non-neutral words were utilized in this study, which were spread equally over three categories; movement-related, pain-related, and positive. The positive words were included to function as a secondary control measure, as the neutral words may be low in saliency as well as low in emotional value. The pain-related words originated from the McGill pain questionnaire, and have been employed in a previous study (van Heck et al., 2017), while the positive and movement-related words were gathered from other studies (Peters, Vlaeyen, & Kunnen, 2002; Roelofs et al., 2005).

These non-neutral words were paired with neutral words, which were sourced from the subtitle database maintained by the Centre for Reading Research of Ghent University (Keuleers, Brysbaert, & New, 2010). Non-neutral words were matched with neutral words based on word type, length and usage frequency. A total of 225 neutral words were employed in creating 75 matched non-neutral pairs, and 75 neutral filler pairs. This list was passed to three native Dutch speakers for additional verification, who determined if the meaning of the words was appropriate for use in this study, as well as investigating if the words had any other meanings or unwanted connotations. Trials were generated in a list-based format beforehand, using Matlab®, and manually checked before use.

Every trial consisted of three parts:

1. The baseline period with the fixation cross. This lasted exactly 500ms.
2. The *word*-phase, during which the words appear next to the fixation cross; one word on each side. These words were horizontally aligned and placed with their centres on a fixed distance from the centre of the fixation cross. This phase lasted exactly 500ms.
3. The *post-dot*-phase, where the words were replaced by a single dot, which appeared at the location of one of the two words. In this phase, participants were required to indicate where the dot had appeared as quickly and accurately as possible by pressing one of two possible response buttons. This phase lasted exactly 750ms.

Each trial was separated by a 250ms inter-stimulus interval, during which the fixation cross was shown. The appearance of the dot separates the non-neutral trials into the congruent and incongruent subcategories. If the dot appears at the position of the non-neutral word, the trial is *congruent*, and if the dot appears at the position of the neutral word, the trial is *incongruent*. The three categories of words (*pain*, *movement*, and *positive*) each have these subcategories, while the neutral trials do not as they contain no non-neutral words. The software Presentation® from Neurobehavioral Systems (Version 19.0, www.neurobs.com) was used to run the experiment. RTs were measured using a Logitech G510S Gaming Keyboard, which has a response time less than 2ms and an accuracy of 1ms.

After completion of the questionnaires, participants were told that instruction of the task would be shown on the screen. The experimental protocol started with a short training session, which contained twelve trials of word pairs that would not appear in the rest of the experiment. This training was to ensure the participants understood the protocol and were able to conform to the instructions.

Each participant was exposed to 600 trials, which were presented in two equal blocks of 300, and separated by a one-minute break. Each word in each of the three non-neutral categories (movement, pain, positive) appeared twice in an incongruent trial, and twice in a congruent trial, meaning there were 50 congruent trials and 50 incongruent trials for each non-neutral category. The remaining 300 trials were neutral trials, made up of two neutral words, and acted as ‘filler’ trials to reduce potential crossover effects between non-neutral trials (each non-neutral trial was always followed by a neutral trial).

Participants were asked to reproduce several words during the break and at the end of the experiment, to confirm that the words were read and processed properly.

2.2.4 Analyses

All analyses were performed using IBM SPSS version 22, and graphical analysis was performed using GraphPad Prism version 6.

First, bias indices were calculated for the dot-probe task using an established method (Roelofs et al., 2005; Vlaeyen & Crombez, 1999; Vlaeyen & Linton, 2000). The bias index relies on comparing the responses to congruent and incongruent trials, and can be calculated by using the following formula:

$$\frac{(RT_{tl,dr} - RT_{tr,dr}) + (RT_{tr,dl} - RT_{tl,dl})}{2}$$

Here, RT stands for the mean of the reaction time for a specific stimulus type. The different stimulus types are defined by the letters between the brackets; *t* stands for target, *d* for dot, and *l* (left) and *r* (right) represent the location on the screen.

This direction of the bias is included in the bias index; a positive value means that the reaction time on congruent was *lower* (i.e. the participant was *faster*) than incongruent, and vice versa.

Furthermore, as this study includes three separate types of non-neutral words, there are three separate resulting biases; a movement bias, a pain bias, and a positivity bias.

Potential group differences were explored using independent samples t-tests where normality was not violated, and Mann-Whitney U tests where a normal distribution was absent. To test whether data was normally distributed, the Shapiro-Wilk test statistic was employed together with visual inspection of the data. Comparisons between the groups cover age and educational level to ensure the groups are equal, and TKS, CIS20-R, SAS, PCS, and the bias indices to investigate differences between the groups. The distribution of genders between the groups was tested using a χ^2 -test.

Next, to test whether the attentional biases differ between the groups, a three by two by two-factor GLM was ran with reaction time as the dependent variable, *condition* (word type; movement, pain or positive) and *trial type* (congruent vs incongruent) as within-subject variables, and participant *group* (patient, control) as between-subject variable. In the case of a significant three-way interaction, further two-way GLMs (trial type x group) were planned for each condition separately. The bias is usually represented by the bias index, which is a difference score between the congruent and the incongruent conditions. As a GLM employs difference scores in its calculations, it can use the congruent and incongruent scores directly, where the bias index is represented as the factor 'trial type'.

The next step was to perform Pearson or Spearman (depending on potential violation of normality) correlations to explore the relation of the self-report measures with the bias indices. Using this method, $r^2 > 0.25$ combined with $p < 0.05$ was considered to be significant as well as relevant (Cohen, 1988). This analysis was restricted to the patient sample.

2.3 Results

2.3.1 Exclusions and missing values

Four controls were excluded after the data-gathering phase due to (initially) unreported comorbidity (chronic pain syndrome, cancer, or fibromyalgia), while four patients were excluded due to their CFS not being verified by a specialist or not consistent with CDC criteria. An additional patient was excluded due to an inability to perform the task, and three patients withdrew from the study after data collection.

All participants completed the dot-probe task, the SAS, the TKS and the CIS20-R. Furthermore, the presence of pain was recorded. However, a subset of the patients filled in different variants of the PCS and the SIP during their visit to the Radboud University Medical Centre, which made it inappropriate to compare these patients with the rest of the population. Furthermore, some questionnaires were not filled in by all participants. As a result, some analyses were only possible on subsets of the total population, which results in varying sample sizes in the different analyses. The relevant sample sizes per measure have been reported for all analyses (see tables). Note that it can also be seen that some variables were not normally distributed (see table 2.1).

2.3.2 Descriptives

Of the 44 patients, 13 were men (30%), of the healthy controls 19 were men (33%). See table 2.1 for a full list of the descriptives. Sex distribution was tested using a Chi-square test, there was no significant difference between two groups ($\chi^2(1, N = 111) = 0.018, p = .89$). Age and educational level were also not significantly different between the two groups (see table 2.2)

Table 2.1: Descriptives

Questionnaire	Measure	Patients (n=44, 13 male (30%))				Controls (n=67, 19 male (35%))				Shapiro-Wilk statistic
		Average	Standard Deviation	Missing		Average	Standard Deviation	Missing		
	Age	43.2		13.8	6	41.1	14.6	0		.13
	Education level	6.0 ^a	0.76 (0.25) ^b		20	6.0 ^a	0.80 (0.75) ^b	13		.00007*
Tampa Kinesiophobia Scale (TKS)	Somatic Focus	9.7	2.7		5	8.6	2.8	5		.008*
Tampa Kinesiophobia Scale (TKS)	Activity Avoidance	12.4	3.6		5	11.5	2.8	5		.16
Tampa Kinesiophobia Scale (TKS)	Total score	33.9	7.1		4	31.8	6.3	5		.03*
Checklist Individual Strength (CIS20-R)	Severity	50.0	5.9		1	18.7	8.0	9		.012
Checklist Individual Strength (CIS20-R)	Focus	28 ^a	6.0 (8.75) ^b		1	11.5 ^a	6.4 (5.5) ^b	9		.072
Checklist Individual Strength (CIS20-R)	Motivation	15.5 ^a	5.6 (8.0) ^b		0	7.0 ^a	3.5 (3.5) ^b	9		.076
Checklist Individual Strength (CIS20-R)	Activity	15.2	4.7		1	6.6	3.9	9		.048*
Checklist Individual Strength (CIS20-R)	Total score	107.1	13.0		1	45.7	17.0	9		.03*
Sickness Impact Profile (SIP)	Somatic autonomy	0.0 (0) ^a	0.92 (0.0) ^b		26	-	-	-		.000000*
Sickness Impact Profile (SIP)	Mobility control	3 ^a	1.3 (2.0) ^b		25	-	-	-		.00001*
Sickness Impact Profile (SIP)	Psychic autonomy and communication	5.3	3.4		25	-	-	-		.00003*
Sickness Impact Profile (SIP)	Social behavior	7.3	2.5		25	-	-	-		.0009*
Sickness Impact Profile (SIP)	Emotional stability	2.0	1.6		25	-	-	-		.00003*
Sickness Impact Profile (SIP)	Mobility range	1.3 (0) ^a	1.5 (2.0) ^b		25	-	-	-		.000000*
Somatosensory Amplification Scale (SAS)	Somatosensory Amplification	20.7	8.4		0	13.3	6.2	0		.138
Pain Catastrophizing Scale (PCS)	Rumination	4.1	3.4		29	3.7	3.3	22		.005*
Pain Catastrophizing Scale (PCS)	Magnification	1 ^a	2.0 (3.75) ^b		29	1.0 ^a	1.7 (4.0) ^b	22		.005*
Pain Catastrophizing Scale (PCS)	Helplessness	3 ^a	4.4 (6.8) ^b		29	3.0 ^a	2.9 (6.3) ^b	22		.010*
Pain Catastrophizing Scale (PCS)	Total score	10.5	8.6		29	8.3	7.1	22		.008*
	Neutral RT	439.6	58.2		0	465.7	55.7	0		.217
	Congruent Movement RT	436.5	62.3		0	396.6	57.2	0		.354
	Incongruent Movement RT	433.0	60.8		0	399.1	58.2	0		.301
	Congruent Pain RT	446.2	59.5		0	417.0	59.5	0		.557
	Incongruent Pain RT	440.8	62.7		0	415.9	59.2	0		.147
	Congruent Positive RT	443.4	59.1		0	407.4	57.4	0		.466
	Incongruent Positive RT	439.4		60.0	0	407.4	56.4	0		.803
	Movement BI	-3.5	19.9		0	2.6	12.2	0		.009*
	Pain BI	4.6	20.8		0	-1.1	13.6	0		.00001*
	Positive BI	-4.0		14.9	0	-0.1	13.1	0		.718

^a Due to non-normality of the data, the average is represented by the median instead of the mean.

^b Due to non-normality of this variable, the interquartile range is given in brackets with the standard deviation.

^c This variable is non-normally distributed, but the median does accurately describe the data due to the small range of the variable. As such, the mean is used, and the median is given in brackets

Table 2.2: Group comparisons

	n	Shapiro-Wilk*	F	t	df	U	Sig. (2-tailed)	Mean Difference	Cohen's d	partial η^2
Age (years)	105		1.52	.738	103		.46	2.15	0.12	0.01
Education level	78	.000069***	0.27			640.0	.92	0.00	0.00	
TKS Somatic Focus	101	.0084*	0.013			895.0	.03*	1.10	0.27	
TKS Activity Avoidance	101		6.51	1.442	99		.15	0.92	0.11	0.02
CIS Severity	101	.012*	6.77			0.0	.0000000***	31.35	3.85	
CIS Focus	101		0.18	11.289	99		.0000000***	14.26	1.90	0.56
CIS Motivation	102		11.18	8.080	100		.0000000***	7.33	1.20	0.39
CIS Activity	101		3.03	9.909	99		.0000000***	8.52	1.56	0.50
SAS	111		4.16	5.288	109		.0000006***	7.36	0.77	0.20
PCS Rumination	60	.0051*	0.05			298.0	.50	0.47	0.11	
PCS Magnification	60	.0047**	0.29			334.5	.96	0.13	0.06	
PCS Helplessness	60	.010*	5.12			274.5	.28	1.62	0.33	
PCS score	60	0.0080*	0.92			280.0	.33	2.20	0.22	
Neutral RT			0.003	3.071	109		.0027***	33.81	0.60	0.080
Movement Bias Index	111	.0084*	6.06			1052.5	.011*	-6.11	-0.28	
Pain Bias Index	111	.000041***	4.83			1233.5	.15	5.69	0.25	
Positive Bias Index	111		1.36	-1.450	109		.15	-3.90	-0.22	0.02

* Only significant values are reported here. If a variable is found to be non-normally distributed, then the Mann-Whitney U test is performed instead of a t-test. Also, note that partial η^2 is not calculated when the data is non-normally distributed.

2.3.3 Questionnaires

As can be seen in the table 2.2 all subscales of the CIS20-R differed significantly between the patients and controls, with patients scoring significantly higher than controls on all measures, on average. The SAS also showed a significant difference, with patients having higher scores on average.

The PCS and the TKS subscale scores did not show any statistically significant differences between the groups, with the exception of the PCS Somatic focus subscale, with patients scoring higher than controls, on average.

2.3.4 Dot-probe

For a representation of the RTs of the dot-probe task in all categories, see Figure 2.1. There was a significant difference between patients and controls in reaction times over all categories of words. The differences between categories within groups is where the biases appear, and these can be seen in the bias indices in Figure 2.2.

To analyse these potential differences, a $3 \times 2 \times 2$ factor (condition \times trial type \times participant group) repeated-measures GLM indeed showed a significant effect of condition ($F(1,109) = 44.8$, $p < .001$, partial $\eta^2 = .345$), where post-hoc testing showed movement-related words having the lowest RTs and pain-related words having the highest RTs. There was also a significant effect of group ($F(1,119) = 9.39$, $p = .003$, partial $\eta^2 = .079$). Post-hoc testing revealed a significant slowing in the patients compared to the control group, which is also evident in the raw RTs (see Table 2.1). No effect of trial type was found at this level. There was a significant three-way interaction between condition, trial type and group ($F(2,109) = 4.25$, $p = .015$, partial $\eta^2 = 0.038$).

Reaction times, emphasis on the conditions

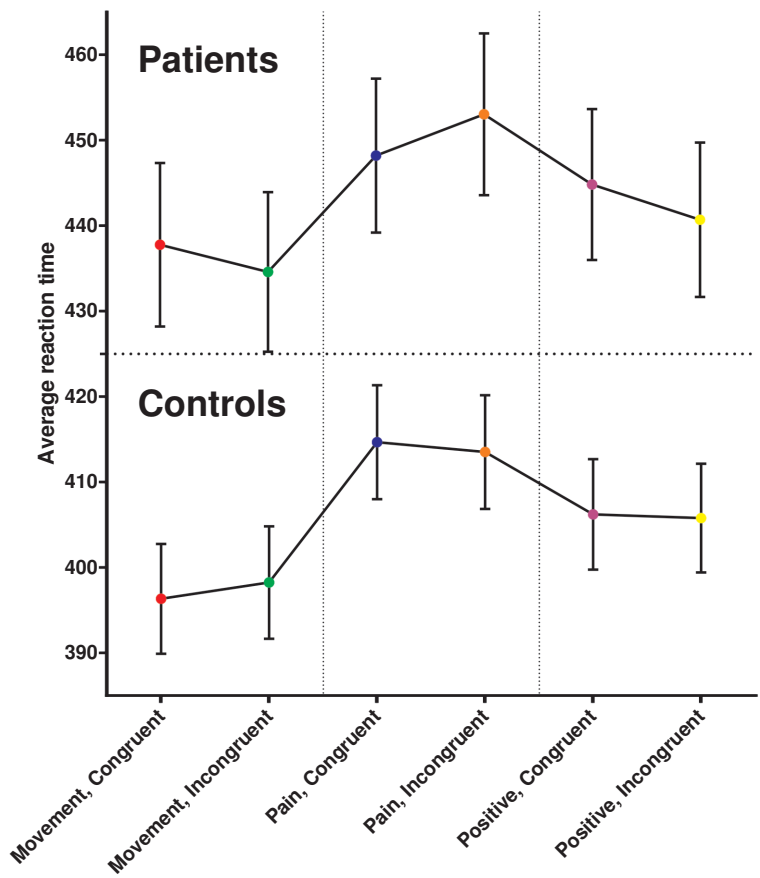


Figure 2.1: Reaction times over the different conditions, where the differences between the trial types (movement, pain, positive) is made visible at the cost of the visibility of the differences between congruent and incongruent.

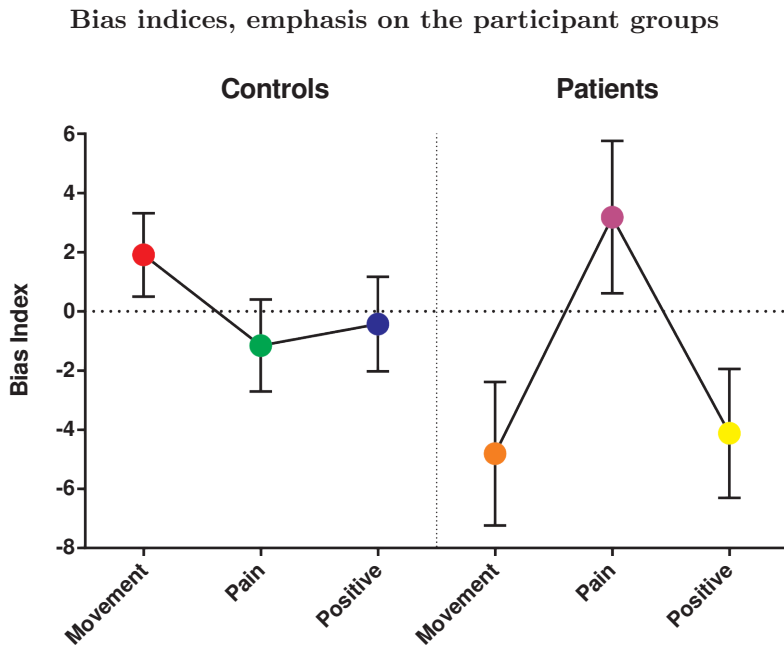


Figure 2.2: Bias indices, calculated from the reaction times, for each trial type, with the two groups shown separately (but on the same scale). Note the increase in absolute bias index as well as the increased spread in the patient group, coupled with the differing biases between the two groups for each of the trial types.

To further examine this three-way interaction, three further 2×2 (trial type \times participant group) GLMs were performed for each condition (movement, pain, positive) separately. Only movement-related words showed a significant interaction between trial type and participant group ($F(1,109) = 4.025$, $p = 0.047$, partial $\eta^2 = 0.036$), although pain-related words showed a trend between trial type and participant group ($F(1,109) = 3.778$, $p = 0.054$, partial $\eta^2 = 0.031$). As can be seen in Figure 2.2, patients responded faster on the incongruent than on the congruent trials, whereas the opposite was found in the control group.

2.3.5 Correlations

As can be seen in the table 3.3, the TKS activity avoidance and the CIS20-R activity both showed a correlation with the positive bias for the patients, but not for the controls. The controls instead showed a correlation between the PCS magnification subscale and the positive bias. Both groups showed a correlation between the PCS helplessness subscale and the positive bias, where a higher score on *helplessness* was associated with a more pronounced bias. Due to the large discrepancy between the patients and controls for the CIS Activity subscale, coupled with the potential descriptive value of this measure, the relationship between the CIS Activity subscale and the bias for movement-related information was investigated in the total population (patients and controls combined). This showed the correlation between the CIS Activity subscale and the bias for movement-related information to be positively related ($\rho(95) = .223$, $p = .03$)

The bias indices did not correlate with each other.

Table 2.3: Correlations

Correlations		Patients			Controls		
		mov_BI	pain_BI	pos_BI	mov_BI	pain_BI	pos_BI
TKS Somatic Focus	Correlation (s)	-.04	.080	.113	.086	.203	.254
	Sig. (2-tailed)	.8	.629	.493	.509	.113	.046*
	N	39	39	39	62	62	62
TKS Activity Avoidance	Correlation (p)	-.017	-.099	.337	-.043	-.129	.197
	Sig. (2-tailed)	.920	.547	.036*	.742	.317	.125
	N	39	39	39	62	62	62
CIS Severity	Correlation (s)	.145	-.173	.048	-.001	.307	.290
	Sig. (2-tailed)	.353	.266	.762	.995	.019*	.027*
	N	43	43	43	58	58	58
CIS Focus	Correlation (s)	-.073	.253	-.089	.175	.162	.150
	Sig. (2-tailed)	.640	.101	.571	.189	.223	.261
	N	43	43	43	58	58	58
CIS Motivation	Correlation (s)	.232	-.043	.251	.103	.177	.031
	Sig. (2-tailed)	.130	.780	.100	.439	.183	.818
	N	44	44	44	58	58	58
CIS Activity	Correlation (s)	.046	-.191	.308	.151	-.017	-.001
	Sig. (2-tailed)	.771	.220	.044*	.259	.900	.995
	N	43	43	43	58	58	58
SAS	Correlation (p)	-.126	.007	.265	.114	-.231	.230
	Sig. (2-tailed)	.416	.962	.082	.360	.060	.061
	N	44	44	44	67	67	67
PCS Rumination	Correlation (s)	-.025	.373	.313	-.054	.083	.244
	Sig. (2-tailed)	.928	.171	.256	.724	.587	.107
	N	15	15	15	45	45	45
PCS Magnification	Correlation (s)	-.162	.195	.328	.057	-.098	.356
	Sig. (2-tailed)	.564	.486	.233	.709	.522	.017*
	N	15	15	15	45	45	45
PCS Helplessness	Correlation (s)	-.014	.249	.589	.040	-.032	.295
	Sig. (2-tailed)	.959	.370	.021*	.797	.836	.049*
	N	15	15	15	45	45	45
PCS score	Correlation (s)	-.115	.366	.491	-.004	.007	.314
	Sig. (2-tailed)	.684	.180	.063	.978	.961	.036*
	N	15	15	15	45	45	45
Movement BI	Correlation (p)	1.000	-.034	.010	1.000	.072	-.053
	Sig. (2-tailed)		.825	.950		.563	.667
	N	44	44	44	67	67	67
Pain BI	Correlation (p)	-.034	1.000	.009	.072	1.000	.077
	Sig. (2-tailed)	.825		.953	.563		.533
	N	44	44	44	67	67	67
Positive BI	Correlation (p)	.010	.009	1.000	-.053	.077	1.000
	Sig. (2-tailed)	.950	.953		.667	.533	
	N	44	44	44	67	67	67

Due to most variables being non-normal, Spearman's Rho is used in all cases.

2.4 Conclusions and discussion

2.4.1 Support for attentional biases

The first goal of this study was to examine potential biases for pain-related words and for movement-related words in patients with Chronic Fatigue Syndrome (CFS).

Aside from a large difference in reaction time, patients also showed a difference in one of the bias indices; the movement BI significantly differed between patients and controls, with patients showing a trend away from movement-related information, which can be termed ‘avoidance’, while the controls showed the opposite for this BI. While we found no significant difference between the two groups on the pain BI, a trend was found that is suggestive of hypervigilance for pain in the patients, and avoidance of pain for controls.

This finding fits within the fear-avoidance model (Roelofs et al., 2005; Vlaeyen & Crombez, 1999; Vlaeyen & Linton, 2000), which predicts avoidance of movement and hypervigilance towards pain. While this model is predominantly used for chronic pain syndromes, it can be extended to CFS for several reasons. Firstly, fear- and avoidance-related beliefs have been noted as the strongest mediator for the effectivity of CBT, suggesting they play an important role in CFS (Chalder, Goldsmith, White, Sharpe, & Pickles, 2015). Second, CFS patients have been known to show altered pain perceptions (Geisser et al., 2008). Thirdly, psychological constructs relevant to the fear-avoidance model, such as catastrophizing, also seem to play a role in CFS (Meeus et al., 2012).

In the fear-avoidance model, avoidance of movement results in less activity, or disuse, which in turn reduces the physical capabilities of the individual. While this presumed association has not been confirmed in CFS, its prominence in the model requires it to be taken into account.

Hypervigilance towards pain has a similar effect, in that it can amplify pain perceptions, which then increase the perceived negativity associated with movement. These phenomena can then be fed back into the fear-avoidance model as increased pain and/or reduced capabilities, which can make the model function as a positive feedback loop, further reducing abilities and amplifying perceptions and pain (Vlaeyen & Linton, 2000).

Surprisingly, no association between fear of movement, as measured with the Tampa Kinesiophobia Scale (TKS), and attentional biases for pain-related words or movement-related words was found. According to the Fear-avoidance model, increased fear of pain should play a crucial role in the presence of hypervigilance for pain-related information, but some studies do not support this association (Peters et al., 2002; Vancleef, Hanssen, & Peters, 2016).

Two of the subscales of the Pain Catastrophizing Scale (PCS), magnification and helplessness, were found to have strong relationships with the bias for positive words, which means that a stronger bias towards positive information can be associated with a more prominent or stronger awareness of subjective helplessness. However, the relationship concerning magnification and the positive bias did not seem to be present in the patients. Catastrophising has been suggested to have a mediating role between positive traits or perceptions and pain perception (Pulvers & Hood, 2013), which the relationship described above supports.

One would expect the PCS to correlate with the pain-related biases, which we did not find. However, the correlation with the positive bias is not fully unexpected; a bias towards positive information or interpretation can balance more negatively-oriented emotions, such as catastrophizing (Fredrickson, 2001; Ong et al., 2010), and this is one of the aspects that cognitive behavioural therapy (CBT) targets (Chambers, Bagnall, Hempel, & Forbes, 2006; Hassett & Gevirtz, 2009). CBT has been shown to be moderately effective in certain cases (Bloot, Heins, Donders, Bleijenberg, & Knoop, 2015; Chambers et al., 2006), and it has been suggested that altered beliefs are related to an improved outcome (Deale, Chalder, & Wessely, 1998; Knoop et al., 2010).

While the fear-avoidance model does not explicitly mention a potential positive bias, it does stand to reason that a bias towards positive information can cancel out or compensate for negative cognitions, such as catastrophizing. However, as we do not find differences between the patients and controls, it is unclear if this compensatory relation is indeed a factor.

2.4.2 Limitations

The two recruitment routes introduced several potential limitations.

Firstly, this could have introduced differences between subsets of patients, which would mean these should not be combined. A t-test showed this to be the case, with patients recruited through social media being both older ($F(1,36) = 5.775, p = .022$), as well as having completed a higher educational level ($F(1,23) = 5.867, p = .024$). However, the basic assumption that these two groups should not be different, may be faulty; the patients that were recruited through the Chronic Fatigue Knowledge Centre in the Radboud University Medical Centre could possibly represent a subset of ‘new’ patients, while the other subset may also include patients that have habituated to the limitations imposed by CFS. In any case, this heterogeneity does benefit the external validity, as no subsets of patients are missed.

Secondly, due to the different environment, some measures were different or missing. For example, in some instances clinical (i.e., shortened) versions of a questionnaire were used. This results in some measures being missing, incomplete, or incomparable, which can increase the risk of type 2 errors.

One frequently stated limitation of dot-probe research concerns the unreliability of the task itself (Kappenman, Farrens, Luck, & Proudfit, 2014; Schmukle, 2005), with potential non-linear relationships (Todd et al., 2015; van Heck et al., 2017), making analysis difficult or near-impossible using classical methods, and contradicting results have been known to disrupt any potential effects in meta-analyses (Crombez, Van Ryckeghem, Eccleston, & Van Damme, 2013). However, the dot-probe task is frequently used, and has been shown to function, often yielding valid and consistent results (Asmundson & Hadjistavropoulos, 2007; Asmundson, Wright, & Hadjistavropoulos, 2005; Baum, Huber, Schneider, & Lautenbacher, 2011; Dear, Sharpe, Nicholas, & Refshauge, 2011; Dittmar et al., 2011; Eldar & Bar-Haim, 2010; Eldar, Yankelevitch Roni, Lamy, & Bar-Haim, 2010; Haggman et al., 2010; Kappenman, MacNamara, & Proudfit, 2013; Keogh, Dillon, Georgiou, & Hunt, 2001; Koster, Crombez, Verschuere, & De Houwer, 2004; Lautenbacher et al., 2010; Roelofs, Peters, Van Der Zijden, Thielen, & Vlaeyen, 2003; van Heck et al., 2017).

2.4.3 Conclusion

Results showed patients to have an attentional bias away from movement-related information, as well as a possible bias towards pain-related information, while controls show the opposite. This is in agreement within the fear-avoidance model of pain. The relationship between activity (as measured through the CIS) and the bias for movement-related information further supports this. These associations support the utility of the fear-avoidance model to CFS, although it is unclear to what extent these findings are associated with pain severity.

Other results, such as the TKS Activity Avoidance and the PCS subscales suggest that the underlying phenomena and relations may be more complex than previously thought (e.g. by indicating potential associations with a bias for positive stimuli). The current study sample was too small to permit more detailed analyses into the relevant associations, and as such further studies are required.

Chapter 3

Interindividual differences in attentional bias patterns for pain-related information

Bias patterns for pain-related stimuli

This chapter is based on:

van Heck, C. H., van Rijn, C., de Kleijn, K., & Oosterman, J. (2019). Interindividual differences in attentional bias patterns for pain (in preparation)

Abstract

Little is known regarding inter-individual differences in attentional biases for pain-related information. For example, whereas some studies indicate that healthy participants may be hypervigilant for pain-related information, other studies have demonstrated primarily avoidance behaviour in their study sample, or reported no attentional bias at all. More knowledge is crucial, since these biases may have significant effects on pain processing.

The present study investigated attentional bias patterns for pain-related information, with specific focus on inter-individual differences in the direction of the attentional bias, distinguishing between avoidance and vigilance. Forty-one participants, aged 21 (SD=2.67, 25 female), were recruited from the local student population. Participants performed a dot-probe task, where neutral and pain-related words were used to create neutral, congruent, incongruent, and double (two pain-related words) trials. They additionally completed self-report measures regarding depression, personality traits, somatosensory amplification, and pain cognitions.

When we examined the participants at a group-based level, no evidence for an attentional bias was apparent. Examination the data at an individual-based level (based on the bias index), revealed several quadratic relationships, where an increase in bias strength relates to an increase in score on several self-report scales, for both directions of the attentional bias. Most importantly, the Pain Anxiety Symptom Scale Fear subscale related to both an increase in vigilance-like and an increase in avoidance-like behaviour.

Based on our findings, we conclude that considering these inter-individual differences could benefit the validity of many studies, specifically for patients suffering from pain and pain-related symptoms.

3.1 Introduction

Pain, more in particular nociception, alerts to a perceived actual or potential immediate threat, and is therefore capable of rigorously directing and manipulating attention (Dittmar et al., 2011; Keogh & Cochrane, 2002; Keogh, Ellery, Hunt, & Hannent, 2001). This connection between pain and attention has far-reaching consequences for the way humans deal with pain and negative concepts. In some cases, attentional biases towards pain can even amplify the pain or the negative sensation (Hakamata et al., 2010; Herbert et al., 2013; Koyama, McHaffie, Laurienti, & Coghill, 2005). Attentional shifts due to nociception are partly bottom-up, or stimulus-driven, processes, and are therefore influenced by the stimulus itself. A light stimulus might not warrant an attentional shift, while a strong stimulus might require conscious effort to keep attention away, or even force a shift towards itself.

However, stimulus-driven attentional shifts are not straightforward; one has to account for many other factors. For example, one participant might shift his attention to one stimulus as soon as it appears, even during demanding tasks, while another participant ignores the stimulus altogether. These individual variations concerning attentional effects have been documented, particularly in pathological conditions. Individual variations concerning attention have been tied to multiple outcomes outside of the field of nociception, such as linking avoidance-behaviour to outcomes in resilience to chronic military stress (Lin et al., 2015). Social phobias have even been linked to both hypervigilance and avoidance (Bögels & Mansell, 2004), both established attentional biases.

In the field of nociception, individual differences have been linked to a pain-related behaviour and processing. For example, anxiety (Herbert et al., 2013), hypervigilance (Baum et al., 2011), and even general personality traits (Lautenbacher et al., 2010) are known to influence perception of pain and disease. Also, more specific outcomes, especially the frequently reported catastrophizing behaviour, have also been linked to pain processing and risk of future pain (Asmundson, Wright, & Hadjistavropoulos, 2005; Keogh & Cochrane, 2002).

Several models have been introduced to explain the development and maintenance of chronic pain. For example, the ‘fear-avoidance’ model suggests the existence of a positive feedback loop, where avoiding pain amplifies or perhaps even creates additional pain, resulting in an increasing disability (Vlaeyen & Linton, 2000). Based on this model, factors such as ‘fear of pain’ and ‘catastrophizing’ play crucial roles in maintaining or exacerbating levels of pain. An alternative model relies on increased vigilance, or ‘hypervigilance’, as an explanation for changes in behaviour in certain individuals (Crombez, Van Damme, & Eccleston, 2005). However, it has been suggested that there might be individual differences associated with hypervigilance, where some individuals are more likely to ‘scan the body for threatening sensations’.

An alternate model, termed the ‘Threat Interpretation Model’, attempts to explain pain processing based on an early vigilance, and a later avoidance of pain-related stimuli. In this model, individual salience or the interpretation of the level of threat of the stimulus is mentioned as a key factor in determining individual vulnerability to the experience of pain, and possibly associated disability (Todd et al., 2015). This is difficult to test, however, but individual susceptibility could possibly be equated to differing personality types, as ‘worrying’, or ‘ruminating’ has been associated with a specific personality type (Ragozzino & Kelly, 2011).

Individual differences seem to play a role in both attentional effects and nociception, but are rarely investigated; there have been studies on individual attentional differences affecting nociception, which link increased vigilance (as hypervigilance) in healthy participants to nociceptive sensitivity (Geringer & Stern, 1986), as well as greater clinical pain severity and sensitivity (Wilner, Vranceanu, & Blashill, 2014). Moreover, individual differences in both avoidance-like behaviour as well as hypervigilance have been shown to be valid predictors of postoperative pain (Goodin et al., 2009; Grosen et al., 2014; Pulvers & Hood, 2013; Wong et al., 2014). However, these studies tend to ignore the differences between attentional biases, and focus on linear correlations, while there is evidence of multiple coexisting attentional biases, with partially opposing directions (Lin et al., 2015)

These partially opposing directions introduce another issue; usually the focus of a study is on group-based differences, where, for example, a selection of patients is compared with a selection of healthy controls. However, if attentional biases can have partially opposing directions, they potentially cancel each other out when examined as a single bias across all participants; this can lead to a false negative (i.e.: no difference between groups), but also a misrepresentation of the groups themselves. This is indirectly supported by the substantial number of studies in healthy participants that show no evidence of an attentional bias in their participants at a group-level (Crombez et al., 2013).

Concluding, there have been several studies regarding individual differences and pain-related behaviour and processing. Some research has been done regarding attentional biases, but the focus has not been on the individual biases, and especially not on polymorphisms in the healthy population. As a result, surprisingly little is known about the potential existence and effect of such inter-individual differences in the attentional bias for pain-related stimuli in healthy individuals, and whether such differences may be similarly evident with regard to factors such as psychological constructs.

Our main aim in this study is to investigate inter-individual differences in attentional bias, and how these differences in attentional bias are associated with psychological constructs.

3.2 Methods

3.2.1 Participants

The study was approved by the Ethic Committee Social Sciences (registered under *ECG2012-1301-005*) of the Radboud University Nijmegen, in accordance with the requirements of the Declaration of Helsinki. All subjects signed a standard written informed consent.

Participants were recruited from the population of healthy Dutch students of the Radboud University Nijmegen, who were required to gather study points through participation in studies. Students not eligible for these points received monetary compensation. Forty-one participants (16 male, 25 female) were included in this study, aged 21 ($M = 21.20$, $SD = 2.67$, $Range = 17-29$).

Participants were subject to exclusion criteria, such as non-normal (not corrected) vision, dyslexia, diabetes, cardiovascular problems, depression, chronic pain (now and in the past), addiction (now and in the past), and pain at the moment of or during the days leading up to the experiment. Participants were also excluded if they were receiving treatment from a medical specialist or were seeing a psychologist, or if they were using psychoactive medication for any reason.

3.2.2 Psychological questionnaires

In order to examine potential subgroup differences, additional questionnaires were included measuring psychological constructs that have been or are expected to be associated with attentional effects and the processing of painful stimuli. The included questionnaires were:

1. The Beck Depression Inventory (BDI), which is designed as a clinical tool to estimate the severity of a depressive disorder, but is also valid to measure sub-clinical levels of depression. Depression has been linked to a plethora of conditions and disorders, including (chronic) pain (Zambito Marsala et al., 2015), and it has been shown to influence attentional biases (Duque & Vázquez, 2015), so it would not be unexpected if it had some relationship with the existence of attentional biases.
2. The Eysenck Personality Questionnaire – RSS (EPQ), which can be classified as a general personality questionnaire, and measures a participant's personality using separate scales: 'social desirability', 'extraversion', 'neuroticism' and 'psychoticism'. This questionnaire was included as several personality constructs, including neuroticism and extraversion, have been linked to experimental pain sensitivity as well as chronic pain (Lynn & Eysenck, 1961).
3. The Pain Anxiety Symptoms Scale (PASS), which tests anxiety-related behaviour and cognition. This questionnaire can also be separated into several subscales estimating elements of pain-related cognition: 'cognitive', 'escape/avoidance', 'fear', and 'physiological'. The PASS has a subscale specific for Fear of Pain, which is a crucial element of the Fear-Avoidance mode (Vlaeyen & Linton, 2000).
4. The Pain Catastrophizing Scale (PCS), which measures elements of catastrophizing behaviour. It can be separated into three subscales: 'rumination', 'magnification', and 'helplessness', which are all constructs associated with catastrophizing. Moreover, 'Catastrophizing' has been associated with pain processing, specifically with the transition towards chronic pain (Keogh & Cochrane, 2002).
5. The Pain Vigilance and Awareness Questionnaire (PVAQ), which can be seen as a measure of generalized attention directed towards pain. This questionnaire is expected to be most suited to detect differing attentional biases, most specifically the 'increased vigilance' - bias (Dittmar et al., 2015).

6. The Somatosensory Amplification Scale (SAS), which can be used as a measure of subjective amplification of sensory input. This questionnaire has demonstrated links with anxiety and depression (Yavuz et al., 2013), as well as chronic pain (Kosturek et al., 1998).

Note that we utilize three separate pain-related questionnaires, which are expected to overlap heavily. However, these questionnaires do represent separate factors, which is especially evident in their subscales. For example, fear is a unique part of the PASS questionnaire, while the phenomenon known as ‘rumination’ is a unique part of the PCS. There are many factors concerning pain, and it is not known which is/are best suited for distinguishing between attentional biases. To ensure we are able to identify crucial pain cognition subscales, we included all three questionnaires.

3.2.3 Setup

The experiment was programmed and run through Presentation®, coupled with a stimulus delivery monitor. The dot-probe experiment, as used here, was based on the version described by Keogh (Keogh, Ellery, et al., 2001), using two types of stimuli in four conditions, which will be explained under the *Stimuli*-section. Reaction time was measured using a Logitech G510S Gaming Keyboard, which has a response time less than 2ms and an accuracy of 1ms.

3.2.4 Stimuli

Pain-related words have been used as a participant-friendly alternative to actual pain (Dear et al., 2011), and there is a large field of research dedicated to their saliency and emotional processing (Blaut et al., 2013; Roelofs, Peters, Zeegers, & Vlaeyen, 2002). Hence, words were used as stimuli for this experiment.

Sixty pain-related words were used, which were partially sourced from the validated Dutch version of the McGill pain questionnaire (Moors et al., 2012), and partially from previous studies. No words needed to be translated, and all words were passed to three native Dutch speakers for verification of their meaning and usage. The pain-related words were all adjectives, with their lengths conforming to a normal curve ($M = 8.7$, $SD = 1.5$). As expected, their valence and arousal ratings, based on the database generated by Moors et al (Moors et al., 2012), were higher than those of the neutral words (see next paragraph).

The neutral words were sourced from the Dutch subtitle database maintained by the Centre for Reading Research of Ghent University (Keuleers et al., 2010). All neutral words were required to be adjectives, and were matched in length and usage frequency to the pain-related words. Words with multiple meanings or alternative interpretations were removed, and the resulting list was passed to three native Dutch speakers for additional verification. A total of 209 words remained for use as neutral stimuli (see supplementary material).

As is common in a dot-probe experiment, we included congruent, incongruent, and neutral trials. In a non-neutral trial, one would see a pain-related word on one side of the monitor, and a neutral word on the other. If the subsequent dot appears on the position of the pain-related word, the trial is 'congruent', and if the dot appears on the position of the neutral word, the trial is 'incongruent'. To establish a proper baseline condition, neutral trials need to be included, which are made up of two neutral words.

Under these circumstances, it is imperative that the neutral words have a very low saliency, with the ideal neutral word having no saliency at all. In this experiment, we employed a large number of neutral words, but every neutral word did appear more frequently than the pain-related words. It is likely that repeating words lowers their saliency, which might influence the results. However, the reduction of the saliency of a word with an already very low saliency is minute, and therefore confounding effects may be negligible.

Also included in the experiment were double trials, where the pain-related words were paired with other pain-related words. For example, a double trial could show *brandend* (*burning*) on the left, and *scheurend* (*ripping*) on the right. Ideally, we would not see a bias towards any specific direction on these trials, but would still see attentional effects due to the nature of the words, when compared to the reaction time on neutral trials. For example: participants displaying increased vigilance might react even faster, due to there being two painful stimuli, but might also show slowing compared to the reaction times of congruent trials, since they are triggered to monitor two potential locations.

The words were presented in 24pt Times New Roman, on a 23" 100Hz LCD monitor using 96DPI, which was situated 65cm in front of the participants. The distance of the participant to the monitor was checked during every break, and no significant movements were observed during the experiment.

3.2.5 Protocol

To ensure cognitive processing of the words took place, we explicitly told the participants there would be a (custom, word-related) questionnaire concerning the presence and frequency of some of the words that appeared in the test, while implying that this questionnaire is a crucial part of the experiment. This was not just a ploy to motivate participants to pay attention to the words; we gathered measures of valence using 5-point Likert scales for a selection of all used words from a database (Moors et al., 2012), to verify consistency between the valence values generated by the subjects and the valence values present in the database. Using this method, we found no reason to exclude certain participants, or even certain words.

At the start of the experiment, the participant was placed in a semi-separate part of the room, and left alone to fill in the first set of questionnaires: a general questionnaire (which records age, gender, and societal factors such as education, as well as exclusion factors), the BDI, and the EPQ. After a set of preparatory exercises including a short training exercise, the participant was asked to start the experiment. The experiment was ordered into four blocks, and contained three breaks of five minutes.

Each trial of the task started with a fixation cross in the centre of a computer screen, which was presented for a minimum of 1500ms, and a maximum of 2000ms. Following this, two words were presented simultaneously, one on the left and one on the right from the centre. These words were horizontally aligned, and placed with their centres on a fixed distance from the centre of the fixation cross (see figure 3.1).

These words were presented for 500ms, after which they disappeared and a dot appeared at the location of one of the two words. It is commonly assumed this timing is appropriate to elicit attentional biases, based on the presence of attentional biases in previous experimental studies (Keogh2001) , as well as the timeframe of peaks in word-related event-related potentials (Marinković, 2004).

Participants were required to indicate where the dot had appeared as quickly and accurately as possible by pressing two of four possible response buttons, using both hands (see figure 3.2). The reason for this was the simultaneous recording of EEG, which was part of another study. This was an attempt to ensure clean and easy-to-interpret EEG data, by (partially) eliminating lateralized motor activity.

The reaction time of both hands was recorded for each trial, and was averaged into a single value for analysis.

An example of a trial

Onzijdig + Stekend

Figure 3.1: an example of a trial (note: this image is a negative), using a neutral word (onzijdig, meaning not being of a specific gender) and a pain-related word ('stekend', meaning 'stabbing' or 'a stabbing sensation'). This trial can be a congruent or an incongruent trial, as there is one non-neutral word, but the location of the dot is not yet known.

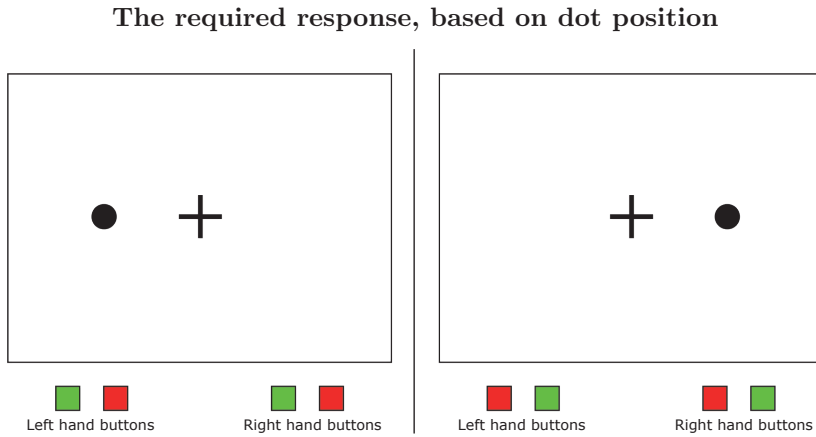


Figure 3.2: The desired response based on dot location. The green buttons designate the 'correct response' buttons.

Before starting the experiment, a short training exercise was performed. This was done to ensure participants understood the instruction, but also to confirm they were reading the words. To investigate this in an easy manner, we included several simple word-jokes in the training exercise, which usually elicited a reaction. All participants were asked if they could reproduce some of the words, even if they showed a reaction during the training exercise.

During visual presentation, the pain-related words were either paired with neutral words, for the 'single' trials, or with each other, for the 'double' trials. To ensure that participants could not predict the appearance of a non-neutral trial, all non-neutral trials were interspersed with a random number of neutral (consisting of two neutral words) trials, as filler trials. Trials which include a pain-related word are higher in salience, which has been known to affect the following trial or trials (Frings, Englert, Wentura, & Bermeitinger, 2010). To reduce this effect on the neutral trials, a minimum of four neutral trials was used as filler trials. This required every neutral word appearing several times, with a maximum of six appearances per neutral word.

Neutral words were randomly selected, and were not allowed to repeat within ten consecutive trials. Moreover, the chance a neutral word was picked was lowered after every occurrence, ensuring that each neutral word would appear in somewhat similar numbers for all participants. Since the number of neutral (filler) trials between non-neutral trials was random, the total number of neutral trials differed slightly between subjects; on average, subjects were exposed to 220 neutral word pairs ($SD = 10$).

Every pain-word appeared once on the left, and once on the right of the dot for every participant. Additionally, every pain-word appeared once in a single trial, and once in a double trial. Since a total of 60 non-neutral words were used, this resulted in each participant being exposed to 60 single (30 congruent/30 incongruent) and 30 double trials.

The lists were generated beforehand for all participants, using Matlab®, and checked manually before use.

When the protocol was finished, the participant was asked to fill in the remaining questionnaires, which included the pain-related questionnaires and a custom word-related questionnaire. This latter questionnaire was administered to ensure the participant was not aware of the reasoning behind the experiment.

3.2.6 Bias index

To determine the strength and direction of the attentional bias, the bias index is commonly used. This index relies on comparing the responses to the congruent and incongruent trials, and can be calculated by using the following formula:

$$\frac{(RT_{tl,dr} - RT_{tr,dr}) + (RT_{tr,dl} - RT_{tl,dl})}{2}$$

Here, RT stands for (in this case; the mean of) the reaction time for a specific stimulus type. The different stimulus types are defined by the letters between the brackets: ‘t’ stands for target, ‘d’ for dot, and ‘l’ (left) and ‘r’ (right) represent the location on the screen. This method has been used before (Asmundson, Carleton, & Ekong, 2005; Asmundson, Wright, & Hadjistavropoulos, 2005; Haggman et al., 2010; Roelofs et al., 2005; Sharpe et al., 2009). Attentional biases can have a positive or negative direction:

1. Participants with a *positive bias*, who respond *faster* on the *congruent trials* than on the *incongruent trials*. These participants primarily display increased *vigilance*.
2. Participants with a *negative bias*, who respond *faster* on the *incongruent trials* than on the *congruent trials*. These participants primarily display *avoidance*-like behaviour.

3.2.7 Analyses

Statistical analyses were performed using IBM SPSS version 22, and graphical analyses were performed using GraphPad Prism version 6.

Next to the bias index, difference scores of the reaction times were used, which were created by subtracting the reaction time (per individual, per condition) of the neutral from the other conditions (e.g., reaction time on congruent trials – reaction time on neutral trials). This corrects for individual differences in baseline reaction speed, and allows us to easily determine if the different conditions show slowing or speeding on the congruent or incongruent trials. In other words, the neutral condition is used as a baseline.

It should be noted that speeding or slowing on specific conditions can mean different things; slowing on congruent trials would mean *increased* avoidance for the individuals displaying avoidance-like behaviour, while it would mean *decreased* vigilance for the individuals displaying increased vigilance. In using difference scores, care has to be taken to recognize the direction of differences between reaction times, and understand what this means in terms of the attentional bias.

Firstly, to test whether an attentional bias can be demonstrated at a group-based level, a 4-factor (condition) Repeated-Measures (RM) Generalized Linear Model (GLM) was run on the entire study population, with reaction time as the dependant variable and condition (neutral/congruent/incongruent/double) as a within-subject variable. Separate RM – GLM's were performed to investigate the possible effects of handedness.

Second, Spearman rank correlations were used to explore the relation of the self-report measures with the reaction times on congruent and incongruent trials. Due to the fact that most self-report measures were non-normally distributed, and the number of participants was low, we opted for nonparametric methods.

Third, and finally, the relationships between the reaction times and the self-report measures were investigated, using visual methods combined with linear and non-linear regression.

We define outliers as being more than four standard deviations away from the mean. Based on this, we found no outliers, and therefore did not see the need to remove data points from our analyses.

3.3 Results

3.3.1 Reaction times

The mean of the reaction times of the neutral trials was 491ms (SD = 66ms), the congruent trials had a mean of 493ms (SD = 67ms), the incongruent trials showed a mean of 487ms (SD = 66), and the double trials demonstrated a mean of 488 (SD = 68). The reaction times did not differ significantly between genders or ages ($p \gg 0.05$).

To ensure reliability, a split-half reliability analysis was performed using the following method: the data was randomly subdivided into two parts, and the two parts were then compared using the split-half reliability analysis, which yields a correlation. This was done for all conditions separately. All raw values (such as the reaction times on congruent trials) have a high reliability; the lowest p-value detected was $p = 0.11$ (also see supplementary materials, ‘Split-half reliability, and split-half analysis’), so we conclude the data is reliable. Secondly, part of the analysis was repeated on the two halves of the data, to ascertain the findings were robust and consistent (also see supplementary materials, ‘Split-half reliability, and split-half analysis’). The results based on the two halves are consistent with each other, and with the results based on the complete data.

A RM – GLM was used to fully examine possible differences between the four conditions (neutral congruent, incongruent, and double). The RM – GLM did not show a main effect of condition ($F(3,1) = 1.454$, $p = 0.231$). A representation of the congruent, incongruent, and double trials as difference scores (condition – neutral) can be seen in figure 3.3.

Variants of the RM – GLM investigating the handedness or the location of the dot did not show any main effect of these two factors.

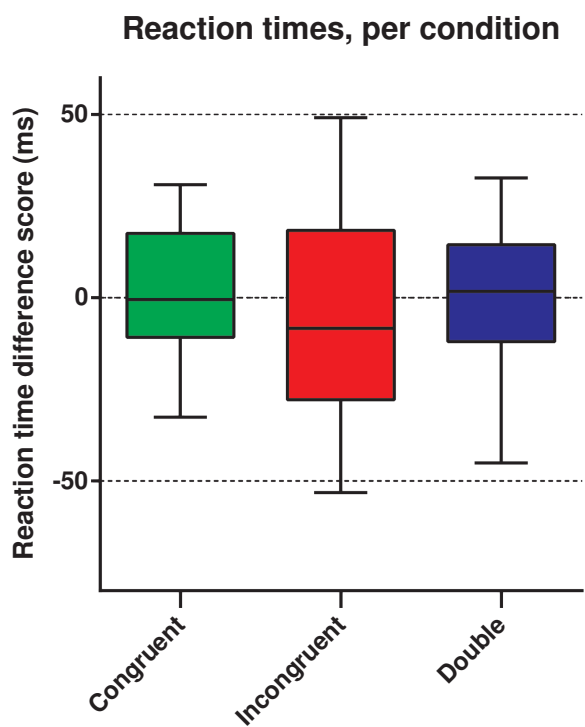


Figure 3.3: Box plots of the reaction times of the different types of trials, with 95-5% percentile whiskers, using difference scores.

3.3.2 Bias index

The bias index, nor the other derived methods showed any significant differences between genders ($p \gg 0.05$, also see supplementary materials, ‘Gender reliability’). Of the group of 41 participants, 15 participants had a positive bias, and thus responded faster on the congruent trials than on the incongruent trials, while 26 participants had a negative bias, and thus responded faster on the incongruent trials than on the congruent trials (see figure 3.4).

Compared with neutral trials, participants displaying avoidance-like behaviour are expected to react slower on congruent trials and faster on incongruent trials, while participants displaying increased vigilance are expected to react faster on congruent trials and slower on incongruent trials (see figure 3.5). Since only the congruent and incongruent trials differed markedly from the neutral ones, only difference scores of these trials were used for subsequent analyses. Since results on double trials were comparable to those on neutral trials, we opted to remove these from the analysis altogether.

3.3.3 Self-report measures

Primary descriptives of the questionnaires can be found in table 3.1. Some of these questionnaires have clinical cut-off values, but these values were not reached in our study, which further shows that we are, at least as far as these measures is concerned, working with a healthy subset of the population.

There was an unequal distribution of genders, which may act as a confounding factor. Therefore, we examined whether there were differences between genders in relation to the self-report measures. Only the SAS showed a significant difference between genders, with a mean difference of 4.1 points in favour of the female participants (also see supplementary materials, ‘Gender effects’).

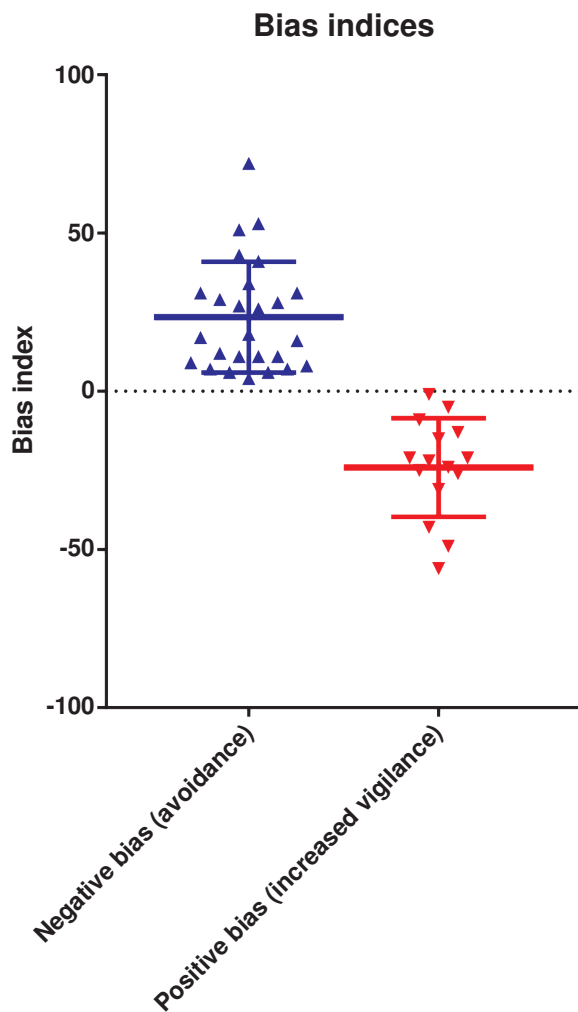


Figure 3.4: Image of the bias index scores of the participants, coloured based on the direction of the bias. The mean and standard deviation are shown as horizontal lines.

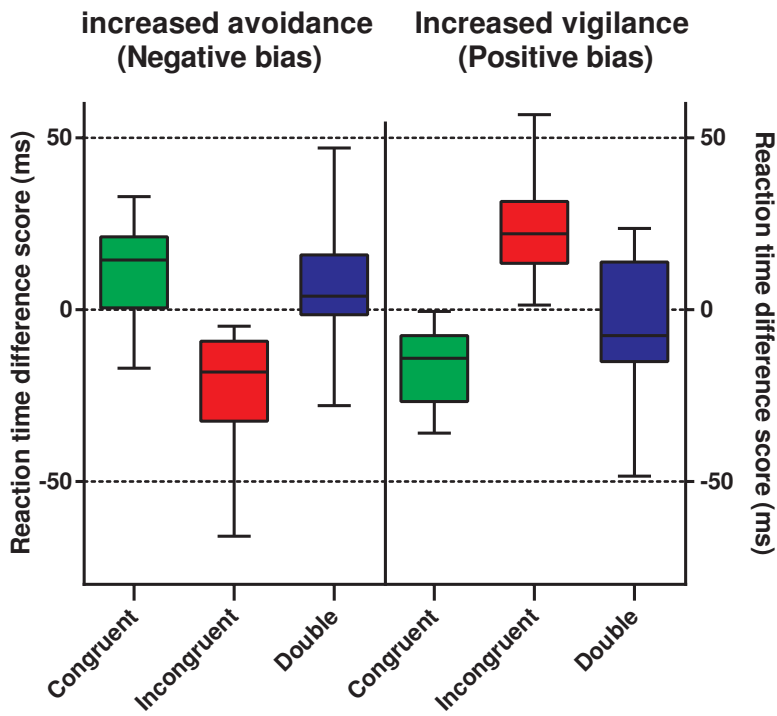


Figure 3.5: Box plots with 95-5% percentile whiskers of the reaction times of the congruent, incongruent and double conditions, which are corrected for the reaction times on neutral trials. This can be interpreted as meaning that the neutral condition for all subjects is 0ms in this figure. Here, we distinguish between a positive and a negative bias based on the bias index, where the two directions of the bias are shown separately.

Table 3.1: Relevant correlations between the reaction time difference scores and self-report measures

Questionnaire / subscale	Mean	Std. Error	Std	Cronbach's α , Corrected Item-Total Correlation
Beck Depression Inventory*	3	0.5	3.4	0.42
Somatosensory Amplification Scale	11.3	0.8	4.9	0.32
EPQ (RSS) Psychoticism*	2.5	0.3	1.8	0.22
EPQ (RSS) Extraversion	8.7	0.4	2.8	0.02
EPQ (RSS) Neuroticism	3.7	0.4	2.4	0.44
EPQ (RSS) Social Desirability	6	0.4	2.4	-0.09
PASS (total)	63.7	4.7	30.1	0.96
PASS Fear*	8.7	1	6.6	0.79
PASS Cognitive	19	1.4	9	0.87
PASS Escape/Avoidance	20	1.4	9.1	0.83
PASS Physiological	16	1.5	9.6	0.83
PVAQ	30.8	2	12.6	0.71
PCS (total)	12.7	1.1	6.9	0.8
PCS Rumination	6.5	0.5	3.4	0.73
PCS Magnification	2.2	0.2	1.5	0.64
PCS Helplessness*	4.1	0.5	3.1	0.66

Excerpt of the correlations found; these denote the measures for which significant correlations were present. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.005$. Note that the critical p-value should be near 0.01, for each group.

The PASS (total), PCS (total) and PVAQ correlated highly with each other ($r = 0.75$, $p < 0.005$), as expected. The BDI showed correlations with the SAS ($r = 0.34$, $p = 0.027$), the PASS ($r = 0.45$, $p = 0.003$), and the PCS ($r = 0.34$, $p = 0.029$). The neuroticism subscale of the EPQ also correlated with these measures with similar values ($r = 0.35$, $p = 0.027$), while the other subscales did not show any significant correlation (the correlations can be found in the supplementary materials, under 'Correlations - total'). As the reliability of the BDI, EPQ, and the SAS was below the acceptable level of 0.7 (see table 3.1), these questionnaires are excluded from further analyses.

3.3.4 Reaction times linked with the self-report measures

Initially, we found no significant correlations concerning the reaction times and the self-report measures, after excluding the questionnaires having low reliability, and after correction for multiple comparisons.

The PVAQ did seem to correlate with the congruent scores, but this correlation was only borderline significant, and did not survive correction for multiple comparisons.

3.3.5 Nonlinear regression

Linear correlations offer a limited view of the relation between two factors, and further investigation is therefore required. To further investigate the attentional biases, we chose to investigate the relationship between the reaction times and the relevant questionnaires in a visual way.

In figure 3.6 the relationships between the incongruent trials (as difference scores) and the PASS (Fear) score is shown as a scatter plot, with a superimposed regression line. Note that the positive and negative bias index scores are coloured, to emphasize their distinct natures.

As can be seen in table 3.2, the relationship between the PASS (Fear) score and the incongruent difference score is best described by a quadratic regression line (as can be seen by the P-value of 0.0002). Furthermore, it describes the data in an acceptable manner, as is evident by the R^2 of 0.34 (adjusted: 0.30).

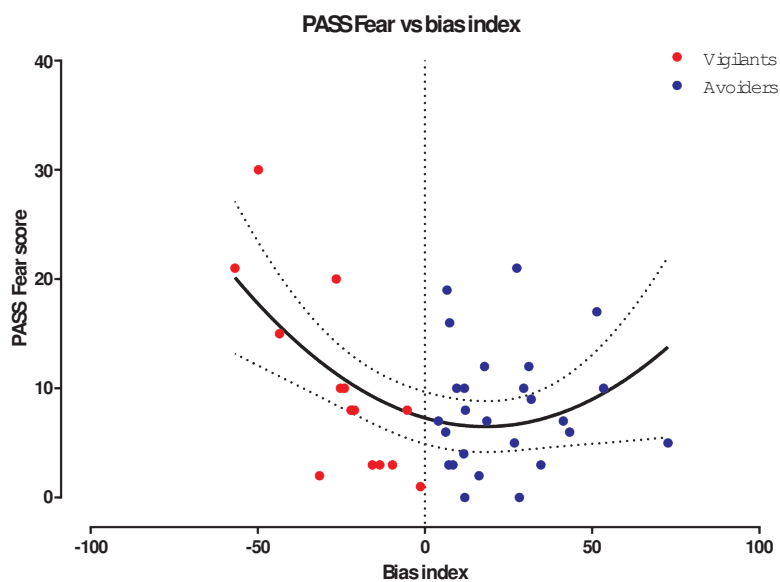


Figure 3.6: Scatter-plot of the incongruent difference score vs. the PASS (Fear) score. The regression line is the best-fit model for all data points. Data points have been coloured based on the direction of the attentional bias.

Table 3.2: Comparisons of regression lines, with goodness-of-fit and best-fit models. Significant relationships are highlighted, as well as noteworthy R^2 values.

Congruent difference score	P value	Preferred model	F (DFn, DFd)	Linear R^2	Quadratic R^2
PASS (total)	0.06	Linear	3.674 (1,38)	0.09	0.17
PASS Fear	0.015*	Quadratic	6.512 (1,38)	0.07	0.21
PASS Cognitive	0.19	Linear	1.750 (1,38)	0.05	0.1
PASS Avoidance	0.07	Linear	3.386 (1,38)	0.04	0.12
PASS Physiological	0.24	Linear	1.407 (1,38)	0.1	0.14
PVAQ	0.1	Linear	2.774 (1,38)	0.12	0.18
PCS (total)	0.25	Linear	1.394 (1,38)	0	0.04
Incongruent difference score	P value	Preferred model	F (DFn, DFd)	Linear R^2	Quadratic R^2
PASS (total)	0.0009***	Quadratic	13.16 (1,38)	0.04	0.29
PASS Fear	0.0002***	Quadratic	16.88 (1,38)	0.04	0.34
PASS Cognitive	0.012*	Quadratic	6.914 (1,38)	0.05	0.2
PASS Avoidance	0.016*	Quadratic	6.365 (1,38)	0.01	0.16
PASS Physiological	0.0020**	Quadratic	11.06 (1,38)	0.02	0.24
PVAQ	0.011*	Quadratic	7.199 (1,38)	0.17	0.3
PCS (total)	0.038*	Quadratic	4.622 (1,38)	0.03	0.14
Bias index	P value	Preferred model	F (DFn, DFd)	Linear R^2	Quadratic R^2
PASS (total)	0.11	Linear	2.757 (1,38)	0.1	0.16
PASS Fear	0.0084**	Quadratic	7.740 (1,38)	0.08	0.24
PASS Cognitive	0.31	Linear	1.055 (1,38)	0.08	0.11
PASS Avoidance	0.15	Linear	2.154 (1,38)	0.04	0.09
PASS Physiological	0.36	Linear	0.8523 (1,38)	0.09	0.11
PVAQ	0.0079**	Quadratic	7.866 (1,38)	0.12	0.27
PCS (total)	0.22	Linear	1.538 (1,38)	0.02	0.05

*: $p < 0.05$, **: $p < 0.005$, ***: $p < 0.001$. Note that the critical p-value for this amount of comparisons, using the Bonferroni-correction, is 0.001.

Only the PASS Fear has a relationship with all reaction-time based measures. The PASS total score, as well as the other PASS subscales, have a relationship with the incongruent difference scores. The PVAQ and the PCS show a similar quadratic relationship with the incongruent difference scores, while the PVAQ also has a relationship with the bias index. It should be noted that in all these relationships, a higher score on a specific (sub -) scale relates to a more pronounced attentional bias. For example, an increase in PASS Fear score is associated with both increased avoidance and increased vigilance, over a low score on the PASS Fear. It should also be noted that following Bonferroni correction for multiple comparisons, the critical p-value is 0.001, which means that only the relationship between the incongruent difference scores and the PASS (total, and Fear) remain.

3.3.6 Correlations per bias direction

We see the previous results as hints towards two separate bias directions, so we opted for a per-direction calculation of simple correlations. In other words, we create separate linear regressions per subgroup for the significant relationships only. Due to the low number of subjects in these subgroups, we felt quadratic or other relationships were inappropriate.

After calculating the correlations of the group of participants showing increased avoidance and the group of participants showing increased vigilance separately, some differences between these two subgroups surface, as can be seen in table 3.3 (all correlations can be found in the supplementary materials, under ‘Correlations – avoidance’ and ‘Correlations – increased vigilance’).

The Pain-related questionnaires do not correlate with the congruent scores in either subgroup. However, these questionnaires do correlate quite well with the incongruent scores, but only in the vigilant subgroup. In the vigilant subgroup, for all three pain-cognition questionnaires the direction is as follows: an increase in pain cognition scores (e.g., pain anxiety) is related to a more pronounced slowing on the incongruent trials ($r \geq 0.60$).

Table 3.3: Relevant correlations between the reaction time difference scores and self-report measures

Primary pain measures (PASS, PCS, PVAQ)		Combined 0.78 > ρ > 0.63 ***	Avoiders 0.73 > ρ > 0.55 ***	Vigilants 0.80 > ρ > 0.76 ***
Congruent RT score	PASS	-0.3	-0.2	-0.5
Congruent RT score	PCS	-0.05	0.2	-0.1
Congruent RT score	PVAQ	-0.33*	-0.1	-0.4
Incongruent RT score	PASS	0.1	-0.3	0.65*
Incongruent RT score	PCS	0.1	-0.2	0.62*
Incongruent RT score	PVAQ	0.3	-0.1	0.73**
Incongruent RT score	PASS Fear	0	-0.38*	0.80***

Excerpt of the correlations found; these denote the measures for which significant correlations were present. *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.005$. Note that the critical p-value should be near 0.01, for each group.

The subscales of the questionnaires were also explored. After correcting the p-values for multiple comparisons ($\# = 12$; corrected $p = 0.05/12 = 0.0042$), a few significant subscales correlations remained. In the vigilant subgroup, the PASS Fear subscale correlates with the incongruent difference score, ($r = 0.80$, $p = 0.0003$), suggesting that an increase in PASS Fear scores is associated with slower responses on incongruent compared to neutral trials. The avoiders show a similar, albeit weak ($r = -0.38$, $p = 0.049$), correlation, indicating that an increase in PASS Fear scores is associated with decreased avoidance, evidenced by slower responses on the incongruent trials when compared to neutral trials.

3.4 Discussion and conclusions

3.4.1 General

Our main aim in this study was to investigate individual differences in the attentional biases in relation to psychological constructs, and look into whether these constructs are associated with the strength and direction of the attentional bias.

Utilizing a dot-probe task, with pain-related and neutral words as stimuli, we exposed participants to neutral, congruent, incongruent, and double trials. When examining the entire study sample, we found no differences in reaction time between the different conditions and no significant association between questionnaires and the reaction times were found.

Using non-linear regression, we found several quadratic relationships between reaction time measures and self-report measures. These relationships demonstrate differing effects dependant on the direction of the bias index. While the direction of the bias is opposite between avoidance and increased vigilance, the effect of some measures seems to be to ‘amplify’ both biases, independent of their direction. For example, an increase in PASS Fear was associated with an increase in avoidance, as well as an increase in vigilance. On the other side, the PCS only seems to have a relationship with the incongruent difference score in the subgroup showing increased vigilance.

A short endeavour into independent attentional biases led us to grouping individuals showing either a positive or a negative bias, and correlating the self-report measures with the reaction times per group. Here, the results primarily show that an increase in vigilance-like behaviour was strongly associated with the pain cognition questionnaires, whereas avoidance behaviour was not significantly correlated with the questionnaires.

In the next sections, we will first discuss the behavioural results (reaction time-related), followed by the relations between the questionnaires and the reaction times. Finally, we will discuss the consequences of these inter-individual differences.

3.4.2 Reaction times

We show here that when examining all participants as a single group, without considering individual differences between the participants, no significant differences between the different conditions are present. At an individual level, however, significant variation between the participants with regard to the direction and strength of the attentional bias was found.

The relationship between the psychological constructs as measured with the questionnaires and the difference scores based on the dot-probe reaction times were assessed. When considering the population as a whole, only the PVAQ and the congruent trials (corrected for the neutral reaction times) seem to correlate, where a higher score on the PVAQ was associated with a faster response on congruent difference scores, which is in turn associated with increased vigilance. This relationship did not survive Bonferroni correction for multiple comparisons, regrettably.

Upon further investigation, quadratic relationships appear; for example, the PASS Fear shows a strong relationship with the reaction time difference score on incongruent trials, but only when utilizing a quadratic regression line. Which are important for several reasons. This means that methods employing linear regression or correlations are blind to these relationships, and would yield false negative conclusions. The relationship between these two measures tells us the following: if the PASS Fear score increases, the strength of the bias (either avoidance or vigilance) increases as well, while the direction of the bias is opposite.

Several pain-related questionnaires show quadratic relationships being a better fit than linear relationships, but mainly on the incongruent difference scores. This is not wholly unexpected, as both attentional biases can affect this reaction-time derived measure. Avoidance would result in a faster response on incongruent trials, as participants are likely to benefit from avoiding the location of the pain-related stimulus. Conversely, while increased vigilance would not result in a slower response on incongruent (compared to neutral) trials, *failure-to-disengage*, which be seen as a part of *hypervigilance* (Sharpe et al., 2009), would.

The PASS Fear shows a relationship in all conditions, which might be due to the PASS Fear being the ‘most accurate’ measure of the attentional bias. This is also not unexpected, since Fear of Pain has been cited as a major player in attentional biases (Keogh, Thompson, & Hannent, 2003). Interestingly, the PVAQ also shows a strong quadratic relationship with the incongruent difference score, which suggests that this reaction-time derived measure might touch upon factors that the PVAQ is specialized in measuring, i.e.; vigilance. Since vigilance is frequently employed in the proposed models of pain, it is not unexpected to see this phenomenon have a relationship with pain processing.

However, the aforementioned method that has yielded quadratic relationships, has a limitation, in that it bases regression lines on the complete data while this may not always be appropriate. It is possible, if not likely, that specific phenomena or measures are associated with only one bias. For example, it is possible that the phenomenon known as ‘rumination’ is only associated with a single attentional bias, which could mean it provides ‘random noise’ in the other attentional bias.

To investigate this possibility, we grouped participants based on the direction of their attentional bias and investigated participants separately, using correlations. Since we are left with very few subjects after this operation, we choose for the more robust Spearman correlations, and would like to state that these results should be interpreted with caution.

Overall, the results show the pain-related questionnaires correlate very strongly with the incongruent scores for the subgroup primarily showing increased vigilance. This means that, for this subgroup, pain cognitions are associated with the attentional bias. A higher score on the pain-related questionnaires correlates with a slower reaction time for incongruent (corrected for neutral) trials, which hints at the possibility of failure-to-disengage to be a major element in this subgroup (Sharpe et al., 2009).

One exception to this finding was the PASS Fear subscale, which correlated with the incongruent difference scores in both subgroups, which is consistent with the earlier found results of the quadratic relationship that the PASS Fear has with the incongruent difference score.

The PASS Fear, as well as the PCS, both fit in the fear-avoidance model of pain, but it is unclear why the PASS Fear outperforms the PCS. It is possible that the PASS Fear is more suited to measure subclinical levels of Fear of Pain, while the PCS performs better when detecting clinically relevant (or perhaps even pathological levels) of catastrophizing. It should be noted that this situation has been encountered before; the PASS seems to perform very well compared with other self-report measures (Dittmar et al., 2011).

3.4.3 Impact of inter-individual differences

This study clearly demonstrates the presence of two attentional biases, which cannot be recognized using linear methods. The PASS (especially the PASS Fear), PVAQ, and PCS (to a lesser degree) show these biases in relation to incongruent difference scores.

This is a strong argument to investigate individuals based on their individual characteristics, with special regard to the different directions of the attentional bias; when looking at a group-based level, the two attentional biases can counteract each other, nullifying any population-level effect, which then leads to erroneous conclusions.

Furthermore, these different attentional biases may show unique associations with diverse psychological constructs, with particularly vigilance being related to pain-related questionnaires. The importance of differentiating between different attentional biases is also supported by findings from outside the pain research field. For example, there is a link between the occurrence of PTSD and attentional biases, where an individual with a specific bias pattern is more at risk for developing PTSD (Lin et al., 2015). This also suggests that such a bias is likely already present before someone develops a specific condition. As a result, in a population comprised of patients suffering from PTSD, this specific bias pattern would be more prevalent. If one would then compare the general population with patients suffering from PTSD, one could conclude that PTSD creates an attentional bias, while it is possible that an attentional bias increases the risk of PTSD. Regrettably, it is difficult to provide definitive proof of a causal relationship in either direction.

The same is very likely true outside of the field of PTSD; many studies hint at, or even directly show links between attentional biases and pain processing. There have been studies that show the presence of a single attentional bias at a group-level in a clinically relevant population (Crombez et al., 2005; Crombez et al., 2013; Herbert et al., 2013; Lautenbacher et al., 2010; Sharpe et al., 2009), while it is not investigated whether all individuals in this population all demonstrate this specific attentional bias. Moreover, these attentional biases, such as increased vigilance (as hypervigilance), failure-to-disengage, and avoidance, have been linked to specific conditions and behaviours. In some cases, these attentional biases may have clinical applications, such as predicting post-operative pain (Lautenbacher et al., 2011; Lautenbacher et al., 2009).

We believe these attentional biases should be investigated on the level of the individual, since the population-level is a mix of individuals showing partially conflicting biases. Furthermore, these biases have different presentations, and likely (partly) different underlying phenomena, which is an argument for splitting the population into separate groups, which can then be investigated fully.

To further investigate the potential neural basis of these inter-individual differences on a group-level, we also recorded EEG during this experiment. The analysis and interpretation regarding the EEG will be described in chapter 4

3.4.4 Limitations

Dot-probe experiments are often used, but the reliability is sometimes seen as low (Schmukle, 2005). However, the dot-probe paradigm does have the capability to yield valid results, as evidenced by studies demonstrating that performance on this task can be used to predict future conditions such as postoperative pain or post traumatic stress disorder. Therefore, it is imperative that reliability measures, such as those produced by the split-half reliability analysis, are gathered, to ensure validity of the results. In this study, reliability of the raw scores (such as the congruent and incongruent reaction times) is high, suggesting the results are valid as well.

On the other hand, split-half reliability of the Bias Index score was low. It should be noted, however, that determining the reliability of derived values, such as difference scores or the Bias Index, can be misleading; a derived value has reduced reliability compared with the raw scores, especially when the raw scores correlate strongly (Webb, Shavelson, & Haertel, 2006). Since in a dot-probe the congruent and incongruent reaction times tend to show very high inter-correlations, the reliability of the Bias Index, which is derived from these two, is expected to be low. Moreover, it has been stated that “low difference-score reliability does not necessarily mean low statistical power for mean comparisons”, as well as “the reliability coefficient for the difference score is often the wrong statistic to use” (Webb et al., 2006). It can be concluded, therefore, that a reliability measure is of limited value, and should be interpreted with caution.

Whereas previous studies employed multiple presentation times of the targets (e.g., 100 to 500ms), including a handful of studies on pain, we used a consistent presentation time of 500ms, which is in line with other studies in this field (Crombez et al., 2013). Moreover, it has been shown through imaging studies that this timeframe consistent with late language components (Marinković, 2004). However, this regrettably limits a detailed examination of the proposed vigilance-avoidance bias that has been reported previously (Baum et al., 2011). According to these studies, many individuals display a pattern of an early (at 100ms) attentional bias towards targets subsequently followed by avoidance at longer presentation times (500ms) (the vigilance-avoidance hypothesis). In the current study, we were not able to examine the possibility of such a response pattern.

Words have been used in many experiments, to good effect. However, this does not necessarily mean that using words is not without issues; subjects have been known to simply not read the words, or to have erroneous (from the perspective of the study) associations with the used words. In the current study we tried to minimize these potential limiting factors by including a memory test after completion of the test session (in order to test whether participants indeed attended to the words, which turned out to be the case) and also by testing that valence and arousal ratings of our selected words were comparable to findings in previous studies. Moreover, the usage of words has been contested from time to time, due to the possibility that words do not provide a deep enough association. For example, the word 'stabbing' might not activate pain schemata associated with pain (Crombez et al., 2013), even though the subject does process the word properly. The fact that there are significant differences between different types of trials (congruent vs neutral, for example) can hint that this is not the case, but this does not exclude the possibility that the activation is different from real-world examples of pain.

Another significant limitation is the sample size. With a total number of only 41 subjects, it is difficult to determine the existence of multiple attentional biases and their relationship with measures such as reaction times and questionnaire scores. Moreover, in small samples outliers can heavily influence the results in small sample sizes. We have attempted to correct for this by employing robust methods and outlier detection, but a larger sample would most certainly be desired in following studies.

Another limitation is that we did not exclude participants based on the magnitude of difference between the congruent and incongruent trials. For example, a participant consistently responding 25ms faster on the congruent trials would be placed in the 'vigilant' subgroup, but a participant responding 1ms faster would also be placed in this subgroup, while this small difference in reaction time might also be an artefact. A possible solution would be to exclusively select participants who show a set minimum difference (as either an absolute threshold, or a percentage-based difference). The downsides of these possible approaches would be the loss of several participants, requiring an even larger sample size. In addition, this would result in the loss of a possible third, potentially relevant, 'bias-free'-group. The potential existence of this third group is relevant for the non-linear aspect of the Bias Index, but is a potential issue in a group-based approach. As such, in the publication dealing with the EEG-aspect of this experiment, participants that did not show any bias (i.e.: the third 'no-bias' subgroup) were excluded.

A potential limitation concerns the presence of a selection bias: the participants were recruited from the local student population, which is not comparable to the general population. For example, these individuals naturally have a higher level of education, which is known to be a critical factor in pain experience and the chronification of pain. It is unknown if or how the level of education interacts with the different subgroups.

Due to the recruitment of students of psychology, our sample consisted of more female than male participants. Firstly, the significant difference on the SAS between genders can be seen as a sign that gender influences the attentional bias, but we found no differences in the actual bias index, or any other value. Therefore, we would state it is unlikely that gender independently influences these biases. Most of the issues with this experiment can be addressed by repetition with a larger set of participants recruited amongst the general population. Additionally, verification of the presence of these or even more attentional bias patterns in clinically relevant subpopulations can aid diagnosis, treatment, and prognosis. Some headway has already been made (Asmundson & Hadjistavropoulos, 2007; Baum et al., 2011; Geringer & Stern, 1986; Herbert et al., 2013; Keogh & Cochrane, 2002; Lautenbacher et al., 2010) but more needs to be done in regard to these different attentional biases and their effects. We especially look forward to seeing the presentation of these, or possibly other, subgroups in clinical subpopulations known to display atypical attentional biases.

Chapter 4

Evidence for a priori existence of attentional bias subgroups in emotional processing of aversive stimuli

Response tendencies or personality traits?

This chapter is published as:

van Heck, C. H., Oosterman, J. M., de Kleijn, K. M. A., Jongsma, M. L. A., & van Rijn, C. M. (2017). Evidence for a Priori Existence of Attentional Bias Subgroups in Emotional Processing of Aversive Stimuli. *Frontiers in behavioral neuroscience*, 11, 87. doi:10.3389/fnbeh.2017.00087

Abstract

Little is known regarding inter-individual differences in attentional biases for pain-related information; more knowledge is crucial, since these biases have been associated with differences in pain processing as well as in predicting the risk of postoperative pain.

The present study investigated EEG correlates of attentional bias patterns for pain-related information, with specific focus on avoidance- and vigilance-like behaviour. Forty-one participants performed a dot-probe task, where neutral and pain-related words were used to create neutral, congruent, incongruent, and double (two pain-related words) trials. EEG was recorded, which was used to generate ERP's of the word-processing phase and the post-dot phase. Participants were placed in two subgroups based on the direction of their attentional bias (either positive; towards the pain-related words, or negative; away from pain-related words). Using t-profiles, four latency windows were identified on which the two subgroups differed significantly.

These latency windows yield areas which correspond with the P1-N1 domain and the P3b for the word-processing phase, while the post-dot phase latency windows cover the areas of the P200 and the P3b. The two subgroups show differences on congruent, incongruent, and the double trials, but interestingly also on the neutral trials. Most notably, the area in the word-phase associated with the P3b is diminished in the subgroup showing a negative bias. The deflections associated with both early and late attentional components, including the P3B, as well as a positive deflection in the timeframe of proposed response evaluation processes differ significantly between subgroups.

In this study we demonstrated that different attentional biases exist in the healthy population, by showing differences in ERP's. We also show differences in processing neutral trials, which suggests there are fundamental differences between these groups in processing words in general.

4.1 Introduction

Nociceptive stimuli are amongst the most prominent and reliable aversive stimuli. As these stimuli alert us to an actual or potential (perceived) immediate threat, they are therefore capable of rigorously directing and manipulating attention (Dittmar et al., 2011; Keogh & Cochrane, 2002; Keogh, Ellery, et al., 2001).

However, individuals have been observed to have attentional biases towards or away from pain and pain-related information. These biases are commonly grouped under avoidance or hypervigilance, based on the direction of the bias. A bias away from non-neutral information can be termed *avoidance*, while a bias towards non-neutral information can be termed *hypervigilance*.

It has been demonstrated that these attentional biases can affect pain sensitivity and augment pain-related behaviours, and both avoidance and hypervigilance have been linked to the processing of pain-related information (Hakamata et al., 2010; Herbert et al., 2013; Koyama et al., 2005; Schoth, Nunes, & Liossi, 2012).

Moreover, these two different attentional biases have clinically relevant implications. For example, hypervigilance has been associated with a high sensitivity to nociceptive stimuli (Geringer & Stern, 1986), leading to higher clinical pain severity (Wilner et al., 2014). In addition, avoidance has been shown to increase the chances of developing chronic pain (Vlaeyen & Linton, 2000), as well as affecting the recovery process (Vlaeyen & Crombez, 1999). Moreover, individual differences in both avoidance-like behaviour as well as hypervigilant behaviour have been shown to be valid predictors of postoperative pain (Goodin et al., 2009; Grosen et al., 2014; Lautenbacher et al., 2011; Lautenbacher et al., 2009; Lautenbacher et al., 2010; Pulvers & Hood, 2013; Wong et al., 2014).

There is also evidence of multiple coexisting attentional biases in the healthy population. For example, it has been demonstrated that a propensity towards avoidance predicted a lower risk of future post-traumatic stress in a population of healthy combat soldiers during training (Lin et al., 2015).

Most documented individual variations are gathered using paradigms based on reaction time (RT) differences. While these are commonly used and a generally accepted method of studying attentional effects, (Baum et al., 2011; Keogh, Dillon, et al., 2001; MacLeod et al., 1986), its use is limited; it cannot show if the attentional bias reflects a transient response tendency to a stimulus or a more general personality trait.

To investigate if participants with different attentional biases differ only in response tendency or show also more general differences in the processing of emotional stimuli, neuroimaging methods might be used. For this, EEG is ideal, as it is an established and proper neuroimaging method, as well as easy to implement in existing experiments. Moreover, by extracting the Event-Related Potential (ERP) from the ongoing EEG time locked to stimulus presentation, inferences about differences in stimulus processing can be made. Furthermore, the distinctive peaks and troughs of these ERPs have been extensively linked to different cognitive processes arising from different functional neural circuits, which has resulted in a wealth of research concerning the relevance and functionality of specific deflections (Luck, 2005b; Nikendei, Dengler, Wiedemann, & Pauli, 2005; Treede et al., 1999).

Most studies of the attentional systems which include EEG focus on a subset of ERP components, mainly the mid-latency ERP components that occur between 50-150ms after stimulus presentation, such as the P1 and N1. Though predominantly determined by the stimulus characteristics, these components are also sensitive towards top-down modulations, such as changes in attention, especially when exposed to stimuli with an emotional content (Lee, Mouraux, & Iannetti, 2009; Van der Lubbe, Buitenweg, Boschker, Gerdes, & Jongsma, 2012). These components also seem to be dissimilar between individuals; high-anxious individuals have been shown to have increased amplitudes of these deflections, while their latencies tend to be decreased.

One of these components, the N1, has been suggested to reflect a sensory gain control mechanism (Luck, Woodman, & Vogel, 2000), and can be observed to be increased in amplitude based on the level of threat or emotional content (Brosch, Pourtois, Sander, & Vuilleumier, 2011; Santesso et al., 2008).

The P1, which normally precedes the larger N1, has been shown to have a similar relationship with emotional content as the N1, but it has also been suggested that this component can be influenced by individual characteristics, such as vigilance (Dittmar et al., 2015). The P1-N1 complex is thought to originate from parietal-temporal-occipital regions, although some results suggest that it may also be generated by frontal regions (Clark, Fan, & Hillyard, 1994).

A later set of components also shows to be affected by emotional content; the N2 component as well as a late positive component were significantly increased based on the 'threat' of the trial (Kappenman et al., 2013). This specific N2 component (as well as the earlier N1) has been used as an indicator of attentional selectivity before (Eimer, 1996). However, the N2 has also been shown to be increased in anxious vs non-anxious individuals, regardless of emotional content in the provided stimuli (Eldar & Bar-Haim, 2010). The N2 is thought to be generated frontally, and may reflect frontal control of the visual system (Luck & Hillyard, 1994).

The late P3 component has been shown to be increased in response to anger-related stimuli, which the authors link to the P3's relationship with target evaluation and response selection (Eldar & Bar-Haim, 2010). The P3 has been linked to late-stage higher-order functions, but recent studies have stated that this component can be separated into the P3a and the P3b, where the first is associated with stimulus-driven attentional mechanisms, while the P3b is more related to event categorisation, attention, memory processing, and target evaluation (Kok, 2001; Polich, 2003, 2007). Moreover, the P3b has been shown to be reduced in amplitude for unpleasant visual stimuli, together with confirming the links between emotional content and the P1 and P2 components (Delplanque, Lavoie, Hot, Silvert, & Sequeira, 2004). The source of the P3b is unclear, but it is commonly found near the parietal areas, and together with the preceding P3a is implied in an attention and/or memory-related circuit pathway between the frontal and the temporal/parietal areas (Polich, 2003).

Studies that have applied EEG to illustrate inter-individual differences concerning attentional biases towards pain-related stimuli are scarce, and yield only few significant results (Dittmar et al., 2011). As a result, there is a lack of knowledge regarding the presence of these biases in the healthy population, while there are indications that inter-individual differences of attentional biases are clinically relevant.

In this report, we explore ERP's of participants performing a dot-probe task using pain-related stimuli. After separating the population based on the direction of their bias (either towards, or away from pain-related information), we will explore possible differences in ERP's.

We employed a dot-probe paradigm in which word pairs were presented, followed by a dot, to which the participant is to respond. The dot appeared at the same location of one of the two words within the word pair, and a delay (or speeding up) in responding to the dot is usually observed due to the direction of the attentional bias combined with the meaning or content of the word. For example, in individuals prone to hypervigilance, a pain-related word might capture attention long enough to show a markedly faster response if a dot is presented at the same location. In contrast; an individual showing primarily avoidance might direct attention away from a threatening word, which would result in a slower response if the dot appears at the location of that word, but a faster response if the dot is presented at the location of the opposite word.

1. The primary goal of the present study was to examine whether differences in attentional bias, based on response latencies to the dot, are already present in the early word-processing phase. Differences in this phase would suggest that there is an *a priori* difference between the two subgroups
2. The secondary goal is to investigate the post-dot phase for similar differences, but then based on the differences between congruent and incongruent trials. Differences in this phase due to increased vigilance or avoidance are expected to be reflected in the ERP components as well.

4.2 Materials and methods

4.2.1 Participants

Participants were recruited from a population of healthy students of the Radboud University Nijmegen, who were required to gather academic credits through participation in studies. Students not eligible for these points received monetary compensation. The study included 41 participants (16 male, 25 female), aged 21 ($M = 21.20$, $SD = 2.67$, Range = 17-29).

Participants were subject to exclusion criteria, such as diabetes, cardiovascular problems, depression, chronic pain (now and in the past), addiction (now and in the past), and pain at the moment of or during the days leading up to the experiment. Participants were also excluded if they were receiving treatment from a medical specialist or were seeing a psychologist, or if they were using psychoactive medication for any reason.

This study was approved by the Ethic Committee Social Sciences (registered under *ECG2012-1301-005*) of the Radboud University Nijmegen, and was performed in accordance with the requirements of the Declaration of Helsinki. All subjects signed a standard written informed consent.

4.2.2 Setup

The dot-probe experiment, as used here, was based on the version described by Keogh (Keogh, Ellery, et al., 2001) (also see the *stimuli*-section). The software Presentation® from Neurobehavioral Systems (Version 18.3, www.neurobs.com) was used to run the experiment. RTs were measured using a Logitech G510S Gaming Keyboard, which has a response time less than 2ms and an accuracy of 1ms.

4.2.3 EEG

We used a standard EEG setup, which consists of a BrainProducts ActiCap 32-channel EEG system. Electro-oculogram (EOG) was recorded using a BrainProducts ExG extension, which ensured the EOG-channels were not included in the common average reference (i.e.: the EOG-channels were not electrically linked to the other channels).

All signals were recorded with a sample frequency of 5000Hz, with the impedance below 20K Ω for all channels. The BrainAmp amplifier has two built-in electronic filters; one high-pass filter of 0.016Hz, and one low-pass filter of 1000Hz. Montage of the electrodes was according the 10-20 system (Oostenveld & Praamstra, 2001).

Due to the dot-probe paradigm consisting of multiple stimuli per trial, the resulting ERP's will be compound ERP's. Therefore, our approach will be partially data-driven, meaning intervals of interest will be localized solely based on their statistical properties. Finally, these regions of interest will be linked to existing research.

4.2.4 Stimuli

We gathered sixty pain-related words from the McGill pain questionnaire and from previous studies. The pain-related words were all adjectives, with their lengths conforming to a normal curve ($M = 8.7$, $\sigma = 1.5$). Comparing their valence and arousal ratings with the ratings of the neutral words, by using the database generated by Moors et al., (Moors et al., 2012), showed their ratings to be higher than those of the neutral words, with a mean valence of 3.9 ($\sigma = 0.8$) versus 2.3 ($\sigma = 1.1$), and a mean arousal of 4.5 ($\sigma = 1.1$) versus 0.7 ($\sigma = 0.3$).

The neutral words were sourced from the subtitle database maintained by the Centre for Reading Research of Ghent University (Keuleers et al., 2010). Only adjectives without additional meanings or alternative interpretations were selected, which were also matched in length and usage frequency to the pain-related words. The resulting list was passed to three native Dutch speakers for additional verification. A total of 209 words remained for use as neutral stimuli (see supplementary material).

As is common in a dot-probe experiment, blocks consisted of congruent, incongruent, and neutral trials. These trials are constructed using two words, one on each side of a monitor (with a fixation cross in the middle of the monitor, see Figure 4.1). The words are shown for a specific amount of time, and then disappear, after which the dot appears at the location of either the left or the right word. Congruent and incongruent trials consist of one neutral word and one non-neutral (in this study: pain-related) word. If the subsequent dot appears on the position of the pain-related word, the trial is *congruent*, and if the dot appears on the position of the neutral word, the trial is *incongruent*. To establish a proper baseline condition, neutral trials need to be included, which are made up of two neutral words.

Also included in the experiment were double trials, using two pain-related words. The reason for including this type of trial was that one could propose that the type of attentional bias influences how such trials are processed. For example, these trials may be perceived as stressful for participants showing avoidance-like behaviour, as they are unable to avoid the pain-related stimulus. Consequently, differences in brain event-related potentials between the two attentional bias groups during presentation of the words can be expected.

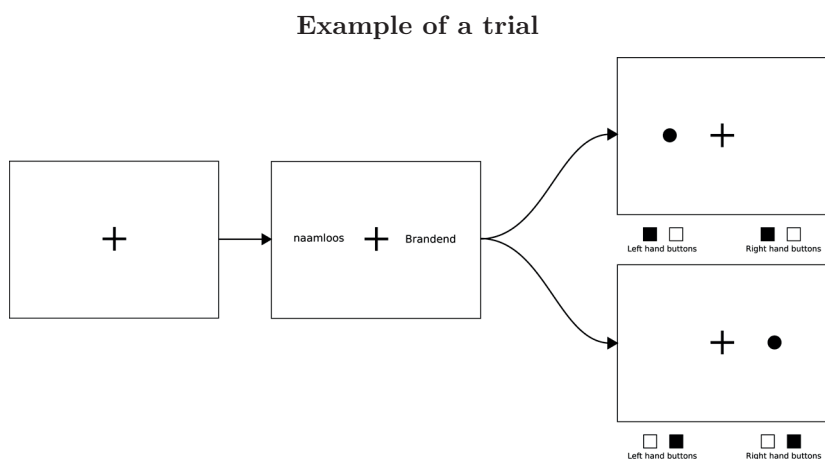


Figure 4.1: An example of a full trial. The first (leftmost) image shows an ‘empty’ screen, with the fixation cross only. The second (centre) image shows a typical non-neutral trial, using a neutral word (‘naamloos’, meaning not having a name) and a pain-related word (‘brandend’, meaning ‘burning’ or ‘a burning sensation’). The two remaining (rightmost) images show two possible outcomes; the top option shows the dot appearing on the left side, which would make this trial an incongruent trial, while the bottom option shows the dot appearing on the right side, which would make this a congruent trial. Note the desired response shown below the two rightmost images; the participant is to respond to the location of the dot with both hands (the correct response is shown as filled squares).

4.2.5 Procedure

To ensure cognitive processing of the words took place, we explicitly told the participants there would be a questionnaire concerning the words at the end. In doing so, we attempted to ensure that the participants paid attention to the words.

The experiment was divided into four blocks, and contained three breaks of five minutes. The impedance was checked during every break.

The trials consisted of the following three parts:

1. A baseline period with just a fixation cross. This period lasted for a minimum of 1500ms, and a maximum of 2000ms. Note that the fixation cross was continually present.
2. A word-phase, during which the words were displayed. As can be seen in Figure 4.1, one word was presented on the left, and one on the right side of the fixation cross. These words were horizontally aligned and placed with their centres on a fixed distance from the centre of the fixation cross. This phase lasted exactly 500ms.
3. The *post-dot*-phase, where the words were replaced by a single dot, which appeared at the location of one of the two words. In this phase, participants were required to indicate where the dot had appeared as quickly and accurately as possible by pressing two of four possible response buttons, using both hands (also see Figure 4.1). Both hands were used to eliminate lateralized motor activity, to make it easier to detect other lateralized activity.

The RTs of both hands were recorded for each trial, and were averaged into a single value for analysis. Trials with large (> 50 ms) differences in RTs between the left and right hand were removed.

During visual presentation, the pain-related words were paired with neutral words, creating non-neutral trials, which can be separated into either congruent (dot on the non-neutral word) or incongruent (dot on the neutral word) trials. The number of neutral trials between the non-neutral trials varied randomly between 1 and 4. Each participant was exposed to a total of 60 non-neutral trials, using all 60 pain-related words once, of which 30 on the left and 30 on the right side of the fixation cross.

Neutral words were randomly selected for each trial, and were not allowed to repeat within ten consecutive trials. Trials were generated in a list-based format beforehand, using Matlab®, and checked manually before use.

It should be noted that participants were not informed about the precise study goals, and all mention of pain-related outcomes (such as through pain-related questionnaires) was saved for the end of the experiment. This was done to ensure the participant was not aware of the reasoning behind the experiment beforehand.

4.2.6 Subgroup split

Two subgroups were created, through the established method of the bias index (Asmundson, Carleton, & Ekong, 2005; Asmundson, Wright, & Hadjistavropoulos, 2005; Haggman et al., 2010; Roelofs et al., 2005; Sharpe et al., 2009). This index relies on comparing the responses to the congruent and incongruent trials, and can be calculated by using the following formula:

$$\frac{(RT_{tl,dr} - RT_{tr,dr}) + (RT_{tr,dl} - RT_{tl,dl})}{2}$$

Here, RT stands for the mean of the reaction time for a specific stimulus type. The different stimulus types are defined by the letters between the brackets; *t* stands for target, *d* for dot, and *l* (left) and *r* (right) represent the location on the screen. This method is commonly used in studies on attentional biases (Asmundson, Carleton, & Ekong, 2005; Asmundson, Wright, & Hadjistavropoulos, 2005; Haggman et al., 2010; Roelofs et al., 2005; Sharpe et al., 2009). Using this, participants can be placed in two possible subgroups:

1. Participants with a *positive bias*, who respond *faster* on the *congruent trials* than on the *incongruent trials*. These participants primarily display *vigilance*-like behaviour.
2. Participants with a *negative bias*, who respond *faster* on the *incongruent trials* than on the *congruent trials*. These participants primarily display *avoidance*-like behaviour.

However, not all participants are expected to show a clear bias; some participants might not have an attentional bias, or might simply not read the words. All participants showing a bias of ten or less milliseconds were termed the *no bias*-subgroup ($n = 9$), and were removed from the analysis.

4.2.7 EEG Analysis

To detect baseline-differences between groups, which may influence our results, 3 minutes of resting EEG was recorded. The frequency properties of the resting EEG of the two groups was compared.

The EEG was analysed using Matlab®, with the Fieldtrip analysis package (Oostenveld, Fries, Maris, & Schoffelen, 2011). A Fourier transform of the resting EEG was used to investigate possible resting state differences between the two groups.

After initial pre-processing, using a 1Hz high-pass filter, and a 40Hz low-pass filter, the EEG was segmented according to trial onset, and baseline correction was applied. Trials were visually inspected for artefacts, and trials found flawed or significantly polluted were removed. Please note that in the whole sequence of events, different time regions were investigated. In order to investigate these different regions, each event was time-locked to different moments. As a result, the baseline correction was repeated several times, each time with a different baseline time-epoch.

For the word-interval, the baseline was defined as -250 to 0 (leading to a total baseline of 250ms), and the investigated interval ranged from 0ms to 500ms, during which the words were present. During the presentation of the words, the congruency of the trial is not a factor, since the dot has not appeared yet, and therefore the congruent and incongruent trials were combined into 'single' trials. As a result, in this interval, there are three conditions; neutral (no pain-related words), single (a single pain-related word), and double (two pain-related words).

Since the dot appears at $t = 500\text{ms}$, the investigated interval post-dot was defined as ranging from 500 to 1500ms. The baseline was set at -500 to + 500, which equates to a full second of baseline over the 500ms word-period as well as 500ms in the period with the fixation cross. This was done to reset the baseline, since the delivery of the fixation cross and the words introduces their own EEG perturbations. The appearance of the dot introduces new information to the subject, which separates the single trials into congruent and incongruent trials. As a result, in this interval, there are four conditions; neutral, congruent, incongruent, and double.

For all forty-one subjects, for each condition, an averaged ERP was produced. To enable pair-wise comparison of the conditions we used t-profiles (Krijzer & van der Molen, 1987), which are t-tests between the sets of individual averages on every time point. We averaged the t-profiles of all conditions into a single Grand Average (GA) t-profile. In this GA t-profile, intervals during which the t-reached significance were identified, which were then used to create latency windows. Only clusters with a minimum of twenty subsequent significant time points were considered as a potential latency window, in order to avoid type II errors.

In the figures, Grand Average ERPs are shown, which are created by collecting the individual average ERPs into a single average. The t-profiles are shown together with the Grand Averages ERPs of both groups.

4.2.8 EEG statistics

Since ERP differences appeared to be maximal over the Pz electrode, which is not unexpected since some of the relevant deflections have been known to originate in the parietal area (Bledowski et al., 2004; Polich, 2007), only the data from Pz were further analysed.

Statistical analysis was performed on values extracted from these average ERPs, using the latency windows provided by the t-profiles. This led to every participant having a single value per condition per latency window.

Statistical analysis of these latency window-based values was performed using repeated-measures GLM's, where the conditions are treated as within-subjects variable and group as between-subjects variable. For the word-phase a 2 (attentional bias subgroup: positive, negative) x 3 (condition: neutral, single, double) GLM was run. For the dot-phase a 2 (attentional bias subgroup: positive, negative) x 4 (condition: neutral, congruent, incongruent, double) GLM was performed. Because the main outcome of the dot-probe paradigm relates to the difference between congruent and incongruent trials, a special contrast will be added which compares the two, as well as contrasts that compare the different conditions with the neutral 'baseline' condition.

4.2.9 Number of trials

After the exclusion of trials containing artefacts, on average 28.9 (SD = 3.90) trials could be used for the congruent condition, and on average 29.2 (SD = 3.54) trials for the incongruent condition. It has been shown that an average consisting of twenty trials is of sufficient quality to base conclusions on (Cong et al., 2011). As such, we are confident there are no issues with the trial counts in making up the averages.

4.2.10 Subgroup properties

Individuals were split into subgroups as explained earlier, with participants showing no substantial bias excluded from both subgroups. The resulting subgroups consisted of 19 individuals with a negative attentional bias, and 13 individuals with a positive bias. See Figure 4.2 for a visualization of the amplitudes in the latency windows, and see Table 4.1 for the average reaction times of the groups for all conditions.

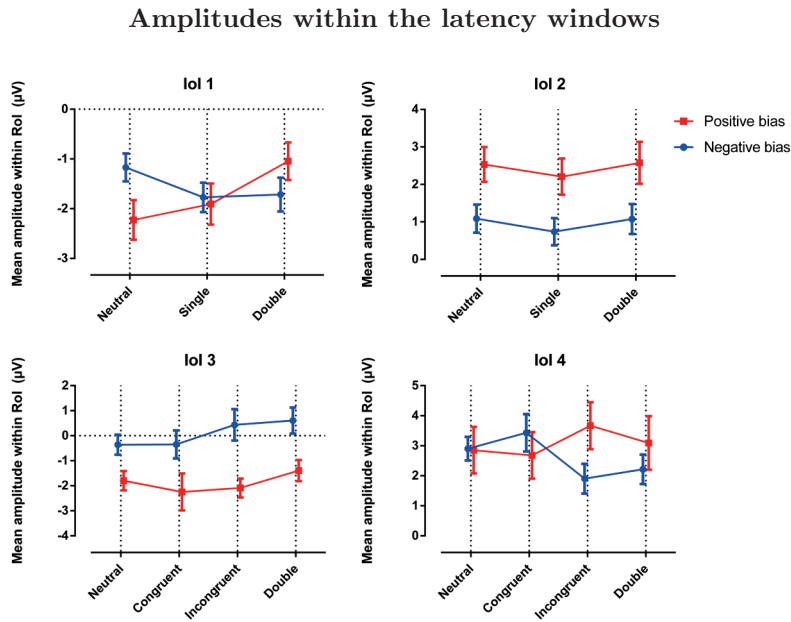


Figure 4.2: The ERP amplitudes within each latency window, for all conditions, for both attentional bias directions separately.

Table 4.1: Reaction times

	Neutral		Congruent		Incongruent		Double	
	mean	std	mean	std	mean	std	mean	std
No bias	460.74	38.81	456.81	37.67	452.68	40.36	453.82	43.63
Positive bias	507.24	57.08	489.45	49.43	517.26	60.23	511.04	57.10
Negative bias	495.98	78.30	513.26	81.66	483.18	71.91	490.50	78.41

Reaction time data for the two subgroups, as well as the *uncommitted* or *no bias* population. Reaction times are shown in milliseconds.

Table 4.2: GLM results

latency window	Condition				Subgroup				Condition * Subgroup				(significant) contrasts							
	Window	df	F	sig.	η^2	df	F	sig.	η^2	df	F	sig.	η^2	where	between	df	F	sig.	η^2	
Word	1	84	92	2.58	1.650	0.20	0.054	1.29	0.19	0.67	0.701	2.58	5.473	0.006	0.16	condition * subgroup double vs neutral	1.29	17.024	0.00028	0.37
	2	376	396	2.58	1.455	0.24	0.048	1.29	8.845	0.004	0.19	2.58	0.007	0.99	0.0004	condition * subgroup double vs neutral				
	3	716	724	2.58	3.175	0.028	0.099	1.29	8.221	0.008	0.22	2.58	1.043	0.38	0.035	condition * subgroup double vs neutral	1.29	9.006	0.005	0.237
Dot	4	900	940	2.58	1.009	0.39	0.034	1.29	0.28	0.60	0.01	2.58	8.616	0.000015	0.229	condition * subgroup incongruent vs neutral	1.29	22.77	0.000048	0.44
																condition * subgroup congruent vs incongruent	1.29	20.946	0.000082	0.419

All relevant results of the GLMs are shown here, split per latency window, and then showing the values for condition, subgroup, and the interaction between the two separately. Significant contrasts are shown as well. Note that the critical p-value is $0.05 / 4 = 0.0125$, since four GLMs are present.

4.3 Results

4.3.1 Resting EEG

Statistical analysis of the Fourier transforms revealed no significant difference in the resting EEG between the subgroups.

4.3.2 Word-phase ERPs

(early) latency window: 84-92ms

88ms after the appearance of the words, the t-profile indicates the presence of a latency window.

A repeated-measures GLM was conducted on the data with *condition* as within-subjects and *subgroup* as between-subjects factor. As can be seen in Table 4.2, this analysis showed no main effect of *subgroup* or *condition*, but a significant interaction of the two. Post-hoc contrasts suggest this difference between the groups to be mainly present on the neutral and the double trials.

ERP's - between groups, neutral trials, Pz

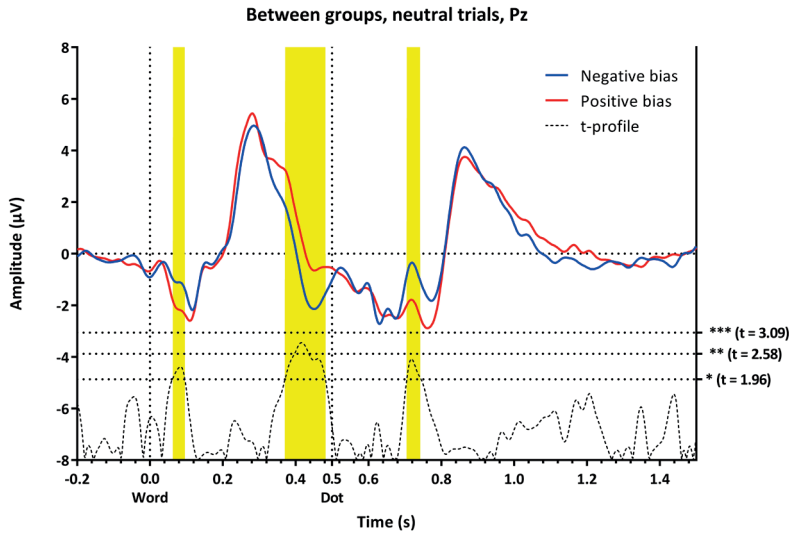


Figure 4.3: The ERP's of the Neutral trials, as recorded from Pz, for both attentional bias directions separately. Latency window 1, 2 and 3 are marked yellow. The dotted line below depicts the t -value (right y -axes) of consecutive t -tests comparing each data point of the Negative Bias Neutral ERP (in blue) against the Positive Bias Neutral ERP (in red).

Figure 4.3 (top left) shows the mean amplitude values in the different conditions, and demonstrates the interaction between *subgroup* and *condition*; the two groups show somewhat opposing patterns, with the neutral trials showing a higher amplitude in the subgroup with a negative bias, the double trials showing a higher amplitude in the subgroup with a positive bias, while the single trials do not show a significant difference. Figure 4.3 shows this latency window in both subgroups for the neutral trials, where the amplitude of the subgroup with a negative bias is more negative than the amplitude of the subgroup with the positive bias.

Figure 4.4 illustrates this latency window within the subgroups. In this figure, ERPs elicited by the neutral trials are compared to the ERPs of single and double trials, in both subgroups. This figure shows differences between the double and neutral trials in the subgroup with the positive bias (lower right panel), with the double trials being less negative, but not in the subgroup showing the negative bias (upper right panel).

Second (late) latency window; 376-396ms

A further comparison of the two subgroups using the t-profiles indicates the presence of one or multiple latency window(s) between 350-480ms in the word-phase in all conditions. Further examination shows the window to be present in all conditions between 376 and 396ms.

A window centring on $t = 386\text{ms}$ with a width of 20ms was analysed with a repeated-measures GLM, with *condition* (neutral, single, and double) within-subjects factor and *subgroup* as between-factor. As can be seen in Table 4.2, there is a marginal effect of *condition*, as well as an effect of *group*, yet no interaction between the two. The value of the subgroup with a negative bias is more negative than the value of the subgroup with the positive bias.

This latency window can be seen in figures 4.3, 4.4, and 4.5 where the subgroup with the positive bias shows a pronounced deflection around 350ms, and a possibly resulting difference in slope afterwards, while the subgroup with a negative bias does not (the deflection is either small, or absent, in almost all conditions).

ERP's - within groups, single and double, both subgroups

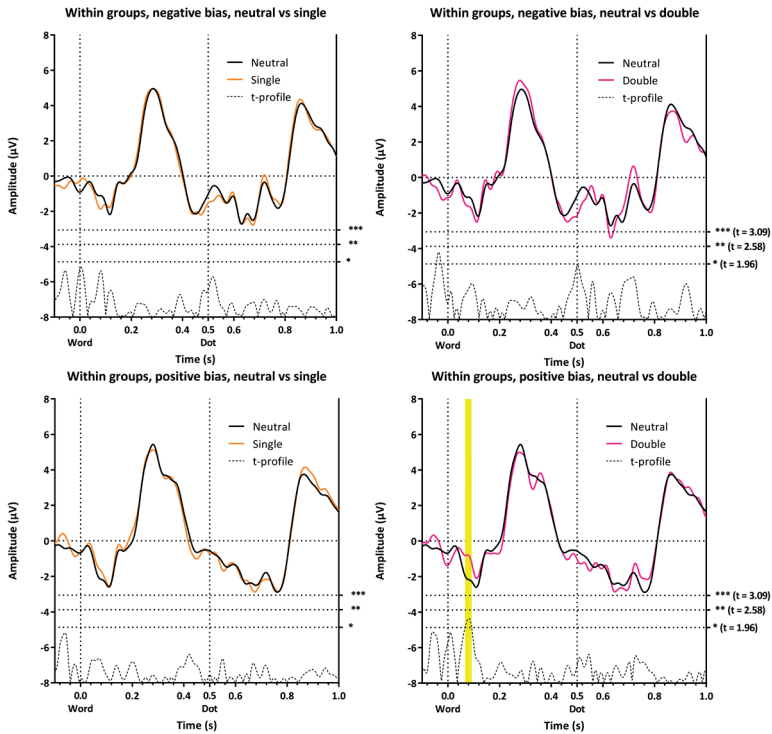


Figure 4.4: The ERP's of the single and double trials, compared with the neutral ERP's. The top two panes show the subgroup with the negative bias, while the bottom two panes show the subgroup with the positive bias. The comparison between the single and the neutral trials is shown on the left, while the comparison of the double and the neutral trials is shown on the right. Note the first latency window only appears on a single comparison, in a single subgroup. The dotted line below depicts the t-value (right y-axes) of consecutive t-tests comparing each data point of the two conditions visible in each respective pane.

ERP's - between groups, congruent and incongruent trials

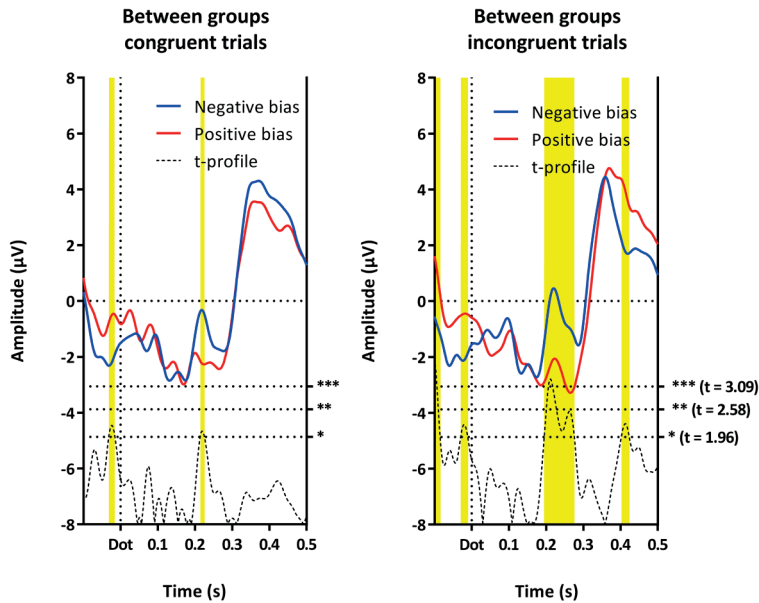


Figure 4.5: Comparison of the congruent and incongruent trials between the two subgroups. Latency window 3 is visible in both conditions, while latency window 4 is only visible in the incongruent trials. Note that latency window 3 is still partially visible. The dotted line below depicts the t -value (right y -axes) of consecutive t -tests comparing each data point of the Negative Bias Neutral ERP (in blue) against the Positive Bias Neutral ERP (in red).

4.3.3 Post-dot ERPs

Third (early) latency window: 216-224ms

At 220ms after the appearance of the dot we find a latency window on Pz in both subgroups. This region is present in all conditions, as can be seen in 4.3, 4.4, and 4.5. This latency window is relatively narrow in the t-profiles, so a window of 10ms is appropriate.

A repeated-measures GLM of this interval on Pz, with *condition* (neutral, congruent, incongruent, and double) as within-factor, and *subgroup* as between-factor, showed a main effect of *condition*, as well as a main effect of *subgroup*, which can be seen in Table 4.1. Further post-hoc contrasts to examine the main effect of condition suggest the most pronounced difference of *condition* to be present between the double and neutral trials.

As can be seen in Figure 4.3, the effect of group can be explained in that the amplitude of the subgroup with a positive bias is more negative than the amplitude of the subgroup with the negative bias (this is also visible in figures 4.4, 4.5 and 4.6).

Fourth (late) latency window, 400-440ms, negative bias

The subgroup showing a negative bias shows a region of interest on Pz 420ms after the dot between the congruent and incongruent trials (see Figure 4.5).

As can be seen in Table 4.1, a repeated-measures GLM with *condition* (neutral, congruent, incongruent, and double) as within-subjects factor, and *subgroup* as between-subjects factor showed no effect of *condition*, nor an effect of *subgroup*, but did show an interaction between these two factors.

ERP's - within groups, congruent and incongruent trials

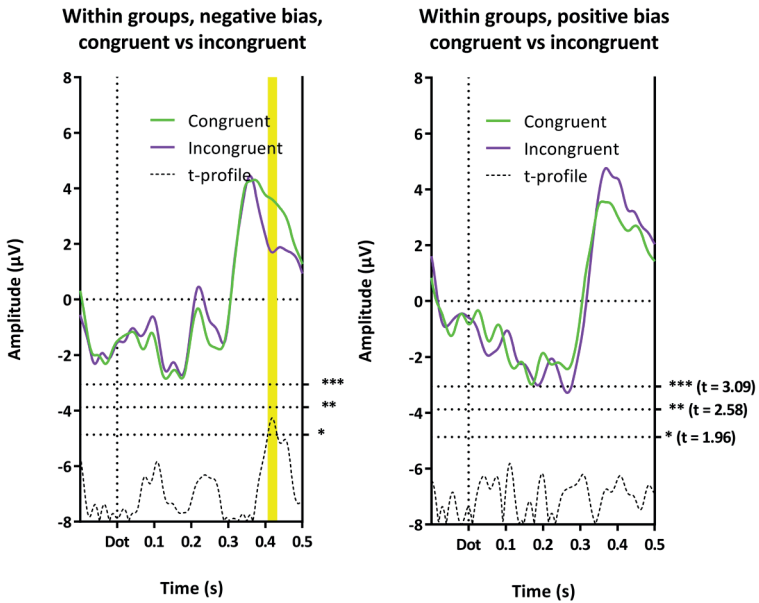


Figure 4.6: Comparison of the congruent and incongruent trials within the two subgroups. Only latency window 4 is visible, and then only in the subgroup showing a negative bias. The dotted line below depicts the t-value (right y-axes) of consecutive t-tests comparing each data point of the congruent ERP (in green) against the incongruent ERP (in purple).

Within-subject contrasts suggest the strongest interaction was present in the comparison between the incongruent and neutral conditions, followed by the comparison between the congruent and incongruent conditions.

When viewing the amplitudes (see Figure 4.3), a pattern emerges; the differences between certain conditions seem opposite in the two subgroups. Most notably, while the subgroup with the negative bias shows the incongruent trials to have a lower amplitude than the congruent trials, the subgroup with the positive bias shows the congruent amplitude to be lower.

4.4 Discussion and conclusion

4.4.1 General

The goal of the current study was to provide support for the existence of two different attentional bias patterns for pain-related information at the neural level.

To be able to do this, we recorded the EEG during the dot-probe task. Using pain-related and neutral words as stimuli, we created congruent, incongruent, double and neutral trials.

No differences in resting state EEG were found, suggesting that the resting states of both subgroups is similar.

4.4.2 Word-phase

During the word-phase, there are three possible conditions, based on the properties of the words involved; neutral, single, or double. As the dot has not appeared at this point, there is no congruency information, meaning the only manipulation here is the level of saliency, or relevance, of the trial.

Very quickly after the words appeared (around 88ms, first latency window), the two subgroups diverge, with the subgroup showing the positive attentional bias (signifying increased vigilance) having a more negative deflection than the subgroup showing the negative attentional bias (signifying avoidance), in the neutral and single trials.

The deflection in this window falls within the classic P1-N1 domain. The amplitude of this component has been known to vary if the participant is instructed to direct attention towards the stimuli (Haider, Spong, & Lindsley, 1964; Naatanen, 1975), and increased top-down attention increases the amplitude of this component (Lee et al., 2009; Legrain, Guérit, Bruyer, & Plaghki, 2002; Van der Lubbe et al., 2012). It has been suggested to be reflective of a frontal sensory gain control mechanism (Luck et al., 2000), which would make it reflective of a top-down control mechanism with the goal of priming the participant. The frontal lobe has been implicated in top-down somatosensory priming before, which is reflected by relatively early components (Wang, Ma, & Han, 2014), such as the components involved in the P1-N1 domain.

As the subgroup showing a positive attentional bias can be seen as having 'increased vigilance', this makes sense; increased vigilance can be read as the subject 'priming' itself using frontal control systems, which it does by pre-allocating more attentional resources to the processing of the words, leading to an increased N1.

This does not explain why this difference also appears on the neutral trials, which shouldn't have any relevance due to their low saliency. Assuming the neutral trials have negligible saliency (this potential issue will be addressed under *limitations*), one explanation may be that the subgroup with a positive attentional bias might display a heightened state of arousal, or attribute additional relevance to words in general, while the other subgroup is not, or might even be predisposed to direction attention from the complete task (i.e.: avoiding the task, by lowering the relevance of the words).

The fact that this group difference was most pronounced for the neutral trials, can be explained by differences in the number of trials; the neutral trials number in the hundreds, while each participant is exposed to thirty double trials. The *single* trials are made up of all trials with a single pain-related word; they are made up of thirty congruent and thirty incongruent trials, as the distinction between the two is non-existent before the dot appears. As a result, the level of noise differs per trial type, with the neutral trials being very low, and the double trials being the highest in noise.

The two groups diverge again on the P3-N4 window (between 350ms to 480ms, second latency window) with the subgroup showing the positive attentional bias having an overall higher amplitude when compared with the subgroup showing the negative attentional bias.

There appear to be two deflections within this latency window; one around 386ms (which can be interpreted as a P3b), and one around 478ms (which can be interpreted as a N450).

However, upon visual examination of the ERPs it seems likely that the perturbation introduced by the first deflection extends into the region of the second deflection. Moreover, the first deflection (the presumed P3b) seems absent in the subgroup showing a negative attentional bias on visual inspection.

Regardless, the two subgroups differ on the P3b, with the subgroup showing a positive attentional bias having a more pronounced P3b in every condition. As the P3b has been associated with event categorisation, attention and memory processing, and target evaluation (Kok, 2001; Polich, 2003, 2007), and the subgroup in which the P3b is more prominent is the subgroup showing the positive attentional bias (which is also known as *hypervigilant*), this would suggest that this subgroup allocates more (attentional) resources to the processing of the stimuli. Similar results have been found before (Bar-Haim et al., 2005). This might be related to the earlier mentioned frontal control systems; not only are the somatosensory components enlarged by priming, but also the later evaluation processing. Moreover, this is consistent with earlier findings (Wang et al., 2014).

4.4.3 Post-dot

After the disappearance of the words, the participant is to respond to the location of the newly-appeared dot. The preceding conditions (neutral, single, double), combined with the dot location, creates four trial types; neutral, congruent (single pain-related word, with the dot on the pain-related word), incongruent (single pain-related word, with the dot on the neutral word), and double trials.

Around 220ms after appearance of the dot, the two groups diverge on all conditions. In this window (around 220ms, third latency window), a peak appears, with the subgroup showing the negative attentional bias having a more positive peak. This interval is where the P200 is expected.

This has been found before, in anxious vs non-anxious individuals (Eldar & Bar-Haim, 2010), which was explained as an increased commitment of attentional resources. As the P200 is more or less established as reflecting selective attention and item encoding, and is commonly associated with frontal top-down control (Dunn, Dunn, Languis, & Andrews, 1998), this is a plausible explanation for the differences between subgroups. The subgroup with a positive attentional bias is marked by being drawn towards the location of the screen that showed pain-related words, while the other subgroup is trying to pull away from this location, which might require additional attentional resources. It is interesting to note that this is also true for the neutral words, which do not incorporate pain-related words.

Finally, there were differences in the subgroup showing a negative attentional bias around 420ms after appearance of the dot. This is a region commonly associated with the P3b. As this deflection is maximal around the parietal region, which is consistent with literature for the P3b (Polich, 2007), it is likely to be indeed the P3b.

In this latency window, the subgroup displaying a negative attentional bias showed a more pronounced P3b in the incongruent trials when compared with congruent trials, while the subgroup with the positive attentional bias seems to show the opposite effect. This is especially apparent when observing Figure 4.3, where the ERP amplitudes follow a specific pattern, which is reminiscent of the RT data on the dot-probe task. The subgroup showing a negative attentional bias is characterized by avoidance-like behaviour, which means they react slower on congruent trials, and faster on incongruent trials. The subgroup showing a positive attentional bias is characterized by increased vigilance which means they react faster on congruent trials and/or slower on incongruent trials.

4.4.4 Limitations

Although the current study clearly shows differences in processing between the two subgroups using EEG, some limitations need to be discussed.

While the ERP's of the congruent, incongruent, and double trials are still quite sufficient, the difference in quality is obvious when viewing the grand averages of the neutral trials; these are the result of large amounts of trials, and are practically noise-free. While this discrepancy is not expected to have any consequences for our conclusions, it should still be said that future experiments would benefit from larger trial numbers in the non-neutral conditions.

The employed method does have a drawback, in that potential interesting differences are missed, which is illustrated by investigating Figure 4.5. Here, the subgroup showing a positive attentional bias does not show significance on the t-profiles between the congruent and incongruent trials. It does show an interesting difference around 770ms (270ms after the dot) on Pz, where a peak has a visibly larger amplitude in the congruent condition when compared with the incongruent condition. This is especially striking, since the preceding negative peak shows the opposite effect, where the amplitude is reduced in the congruent condition. Moreover, this peak is recognizable as a P3a, which has been associated with frontal stimulus-driven attentional systems (Polich, 2007).

Classical methods would ignore these t-profile-based latency windows, and simply utilize literature-based intervals, or manually pick peaks while possibly calculating difference scores between this peak and the preceding negative peak. For example; the positive deflection just before latency window 4 could be combined with its preceding negative deflection in a peak-to-peak-method, which could yield statistically significant results. The benefit of the currently employed approach is that it is highly robust, however, it is insensitive to this specific presentation, and therefore these deflections may be unjustly ignored.

Another potential limitation concerns the reliability of the dot-probe paradigm (Kappenman et al., 2014). One of the few studies on this particular subject yielded only very little significant results (Dittmar et al., 2011), suggesting either the dot-probe paradigm is flawed, or the effects of attentional biases are spurious findings. However, given the wealth of studies utilizing the dot-probe paradigm to good effect (e.g., demonstrating that specific attentional biases predict future conditions, such as postoperative pain), as well as the studies showing attentional biases in other populations, and the success of this study, we would argue that the dot-probe paradigm as well as attentional biases can be made visible in a reliable manner.

The dot-probe paradigm, while used often, can introduce a limitation; participants have been known to simply not read the words, or to have erroneous (from the perspective of the study) associations with the used words. In the current study, we tried to minimize these potential limiting factors by including a questionnaire testing their memory and perception of the words, which was applied after completion of the test session. This test showed the participants did indeed read and remember the words.

Still, the words might not activate the pain schemata associated with pain (Crombez et al., 2013), even though the subject processes the words properly. The fact that there are significant differences between different types of trials (congruent vs neutral, for example) suggests that this is not the case, as subjects process the words sufficiently to evoke these differences, but this does not exclude the possibility that the activation is different from real-world examples of pain.

Additionally, the choice of words can impose limitations as well. In this study, we chose to implement pain-related words, but these might not seamlessly overlap with aversive stimuli. However, we feel this is an appropriate choice as pain-related information is highly aversive. While a broader set of words might cover all possible aspects of aversive information, it would also include additional noise and increase the duration of the experiment.

4.4.5 Future research

Attention is frequently studied using imaging techniques, and as a result there is much known about which areas of the brain contribute to the phenomena of attention (Knudsen, 2007). The separate deflections of EEG can relate to specific brain areas, such as the frontal eye fields, which are areas involved in mediating task-specific functions, and the posterior intraparietal sulcus, which varies its activity with the level or intensity of attention involved (Culham, Cavanagh, & Kanwisher, 2001). Other regions, such as the thalamus, dorsolateral prefrontal cortex, and the basal forebrain are also part of the attentional networks, and fulfil distinct, yet partially unknown, roles (Small et al., 2005). Knowing which regions are active at those deflections can assist in interpretation of these deflections and their underlying phenomena.

However, due to the limited number of EEG channels in the current study, it is not possible to relate ERP activity to any of brain areas, using just the data gathered in this study. As such, we would suggest to include fMRI experiments, or to expand the number of EEG-channels, to allow for source localization in a future study.

4.4.6 In conclusion

In this study, we demonstrated that different attentional biases exist in the healthy population, by showing differences in ERP's. Most notably, the deflections associated with early and late attentional components, including the P3B, as well as a positive deflection in the timeframe of proposed response evaluation processes differ significantly between subgroups.

Moreover, these two biases do not only differ on trials utilizing pain-related words, but also on neutral trials, which suggests there are fundamental differences between these groups in processing words in general. Previously, it has been shown that these two attentional biases can be associated with different response patterns on questionnaires, but now we show that they also differ in basic neural phenomena.

Most interestingly, while the participants are split based on the bias index, which is calculated based on their response times on the dot, we already see significant differences between the groups before the dot appears (i.e., during the word processing phase). This suggests that the two attentional bias groups represent genuine differences in the processing of words, which can already be detected at the word-processing level.

This information is of crucial importance as these biases have been associated with, among other things, the risk of future pain chronification (Lautenbacher et al., 2010). Further investigation into these attentional biases and their effects is expected to yield not just more information regarding the effects of these biases, but also possibly handles for future treatment, as well as a deeper understanding of the underlying phenomena.

Chapter 5

Pain Processing in a Social Context and the Link with Psychopathic Personality Traits

An Event-Related Potential study

This chapter is published as:

van Heck, C. H., Driessen, J. M. A., Amato, M., van den Berg, M. N., Bhandari, P., Bilbao-Broch, L., Farres-Casals, J., Hendriks, M., Jodzio, A.C., Luque-Ballesteros, L., Schöchl, C., Velasco-Angeles, L. R., Weijer, R. H. A., van Rijn, C. M., Jongsma, M.L.A. (2017). Pain processing in a social context and the link with psychopathic personality traits - an Event-Related Potential study. *Frontiers in Behavioral Neuroscience*, 11, 180. doi:10.3389/FNBEH.2017.00180

Abstract

Empathy describes the ability to understand another person's feelings. Psychopathy is a disorder that is characterized by a lack of empathy. Therefore, empathy and psychopathy are interesting traits to investigate with respect to experiencing and observing pain.

The present study aimed to investigate pain empathy and pain sensitivity by measuring event-related potentials (ERPs) extracted from the ongoing EEG in an interactive setup. Each participant fulfilled subsequently the role of 'villain' and 'victim'. In addition, mode of control was modulated resulting in four different conditions; passive villain, active villain, active victim and passive victim. Response-, visual- and pain ERPs were compared between all four conditions. Furthermore, the role of psychopathic traits in these outcomes was investigated.

Our findings suggested that people experience more conflict when hurting someone else than hurting themselves. Furthermore, our results indicated that self-controlled pain was experienced as more painful than uncontrolled pain. People that scored high on psychopathic traits seemed to process and attend to pain differently.

According to the results of the current study, social context and personality traits seem to modulate pain processing and the empathic response to pain in self and others. The within-subject experimental design described here provides an excellent approach to further unravel the influence of personality traits on social cognition.

5.1 Introduction

5.1.1 Pain and empathy

From an evolutionary point of view, pain signals actual or potential injury or damage to bodily parts and is thereby a protective mechanism. Perceived pain severity can be greatly influenced by various factors, e.g. attention and expectancy (Melzack & Wall, 1996). Moreover, it has been determined that pain is perceived as less intense when it is self-controlled (Pellino & Ward, 1998; Salomons, 2004).

Humans are naturally social individuals and experience discomfort while observing another person in pain. This phenomenon, termed as *pain empathy*, is a complex construct that describes the ability to understand another person's situation or feelings (Davis & Davis, 1980; Lietz et al., 2011) and is believed to be one of the requirements for successful participation in current society (Schneider & Ingram, 2005).

Neuroimaging studies focussing on empathy received considerable effort in the past decade (Decety, 2010; Singer & Lamm, 2009). For instance, previous studies showed that ongoing information processing is affected differently when being exposed to pictures that show other person's pain than being exposed to neutral pictures (Avenanti, Buetti, Galati, & Aglioti, 2005; Bufalari, Aprile, Avenanti, Di Russo, & Aglioti, 2007). Evidence from neuroimaging research suggests that experienced pain and observation of pain in others elicit similar activation patterns in brain areas involved in the processing of both affective (e.g. the anterior insula and the medial/anterior cingulate cortex (Decety, 2010)) and sensory (e.g. the primary somatosensory cortex and parietal operculum (Bufalari et al., 2007)) information. These findings support the theory that describes a shared neural network for one's own and others' emotional and sensory experience.

Current models of pain-empathy suggest that empathy-related processes are derived from both bottom-up features and top-down factors (Decety & Moriguchi, 2007). Zooming in on these top-down factors, social context seems to be an important modulator of pain perception in self and others (Decety, Michalska, Akitsuki, & Lahey, 2009; Singer et al., 2006). Several aspects of social context, such as relationships between individuals (Singer et al., 2006) and attitude towards others (Decety et al., 2009) have been studied previously. Studying the lack of empathy with respect to pain might be even more salient.

5.1.2 Psychopathy; a pain- and empathy-related disorder

Certain psychopathic disorders are linked to deviant pain processing and experience. Although the majority of studies have been focused on psychopathy in criminal offenders (Thompson, Ramos, & Willett, 2014), psychopathic personality traits are demonstrated to be normally distributed in the general population (Gao & Raine, 2010; Hare & Neumann, 2008; Levenson et al., 1995). Recent neuroimaging studies have suggested that an attenuated function in the amygdala and anterior insula underlies reduced empathy in individuals with high levels of psychopathic traits (Seara-Cardoso et al., 2015).

Moreover, research revealed that people high in psychopathic traits show atypical neural activity in response to imagining others' pain (Decety, Chen, Harenski, & Kiehl, 2013; Seara-Cardoso et al., 2015). Besides characteristics of lack of empathy, psychopaths tend to experience pain differently compared to non-psychopaths. For instance, Marcoux and colleagues (Marcoux et al., 2014) found a higher pain threshold in people with psychopathic tendencies.

5.1.3 Electrophysiology in pain research

Electrophysiological techniques, such as EEG, can discriminate event-related activity with a high temporal resolution and are therefore excellent methods to study if and when differences in neural signals related to certain events occur. Extracting such event-related activity from the ongoing electroencephalogram (EEG) allows researchers to study event-related potentials (ERPs). ERPs can be elicited by either actions, simple or complex stimuli, or events. This ERP technique allows us to directly study the neural responses associated with specific aspects of emotion and information processing.

5.1.4 The Error Related Negativity

A specific component of the response-locked ERP that is studied in empathy-related research is the error-related negativity (ERN), which is an event-related potential that is associated with an incorrect motor response (e.g. a button press). It starts shortly before the time of an incorrect response and peaks around 100ms thereafter (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1990; Gehring, Goss, Coles, Meyer, & Donchin, 1993). The ERN is generated within or near the dorsal anterior cingulate cortex (Dehaene et al., 1994). Electrophysiological evidence demonstrated an association between the ERN, as electrophysiological correlate of action monitoring, and empathy-related affective responding (Larson, Fair, Good, & Baldwin, 2010; Thoma & Bellebaum, 2012).

According to different theories, the ERN reflects the error-detection process itself (Falkenstein et al., 1990), or an emotional response to the error (Bush, Luu, & Posner, 2000). Regarding the latter, research showed that an increased ERN has been associated with, for instance, concern over the outcome of an event (Gehring & Willoughby, 2002; Gehring, Himle, & Nisenson, 2000). In line, a diminished ERN has been associated with a lack of concern over the outcome of an event (Santesso & Segalowitz, 2009).

5.1.5 Visual ERPs

Visual stimuli result in a series of peaks in the EEG and thereby determine the visual ERP. Perhaps the most studied component with respect to a wide range of cognitive processes is the P300 component (or P3). This visual P3 component is modulated by cognitive processes such as expectancy, relevance, meaning and attention (Gray et al., 2004). Several studies found that viewing painful stimuli caused a larger visual P3 amplitude over the posterior parietal area compared to viewing neutral pictures (Fan & Han, 2008; Meng, Hu, et al., 2012).

5.1.6 Pain ERPs

Previous literature on empathy is mostly based on studies in which participants are not exposed to actual pain or pain in others directly (Botvinick et al., 2005; Singer et al., 2004). A more realistic, though controversial method, would be to introduce real-life situations of pain experience. Such experimental setups are not very common. One famous example stems from the controversial Milgram experiment that studied obedience (Milgram, 1963).

In the current study, we adapted this approach to investigate the processing of painful stimuli delivered to oneself or to another person in both an active and a passive condition. Electrophysiological methods are useful in obtaining objective measures of clinically and experimentally induced pain and have proven to be successful in characterizing ERPs elicited by painful stimuli (Iannetti, Zambreanu, Cruccu, & Tracey, 2005).

Previous studies reporting pain ERPs describe an ERP that consists of a negative wave followed by a large positive wave that occurs ca 400 ms after pain onset (Iannetti et al., 2005; Vossen, van Breukelen, Jimvan, Hermens, & Lousberg, 2011). This positive peak has been labeled differently by different studies, e.g. as a P2 (Iannetti et al., 2005) or as a P3 (Vossen, 2011). In addition, this late positive component has been reported to be increased with when the subjective pain experience is more intense and is generated by the cingulate gyrus (Iannetti et al., 2005). Thus, it has been proposed that this component can be used as an objective measure of experienced pain (Bromm, 1995; Chen, Richard Chapman, & Harkins, 1979).

5.1.7 The present study

In the present study we investigated pain- and empathy-related neuronal responses in a socially interactive setup. The main aim of this experiment was to investigate the differences in neuronal responses with respect to the participants' capacity (active/passive) when observing someone in pain or receiving a painful stimulus. Therefore, we designed a paradigm that included four conditions. During the first condition (*passive villain*) the participant passively watched another person pressing a button. During the second condition (*active villain*) the participant had to press the button him- or herself. During the third condition (*active victim*) the participant received the electrical shocks after pressing the button him- or herself and during the fourth condition (*passive victim*) another person was pressing the button while the participant was receiving the electrical shocks. In addition, we asked participants to fill in a self-report questionnaire to measure psychopathic traits in order to investigate the role of psychopathic personality traits on pain- and empathy-related neuronal responses.

We studied four contrasts in this paradigm. The first contrast compared the ERN of the response-locked ERP of the active villain versus the active victim. This enabled us to study the amount of conflict the participant is experiencing when hurting himself or another person. We expected the active villain to show an increased ERN compared to the 'active victim'. Since psychopaths are characterized with low empathy, we expected that this effect correlated negatively with psychopathic traits.

The second contrast considered the potential difference between passive and active observing of another person in pain. The visual P3 component of the visual ERP of the passive villain versus active villain were compared. We expected a higher visual P3 component for the active villain compared to the passive villain condition, since the active role creates a more involved and responsible position for the villain. In line, we expected a negative correlation with psychopathic traits- with the magnitude of the visual P3 effect. The third contrast compared the visual P3 component of the visual ERP of the active victim versus the passive victim. This enabled us to study the role of having control over pain. Losing control over a threatening situation increases attention/vigilance which results in an increased visual P3 component, therefore we expected to find higher visual P3 components for the passive victim compared to the active victim. We did not expect this contrast to be linked to psychopathic traits.

Also the fourth contrast is related to control over pain. We compared the late positive pain component of the pain ERP of the active victim versus the passive victim. It has been demonstrated that pain is perceived as less intense when it is self-controlled (Pellino & Ward, 1998). This effect is reflected in attenuated neural responses in reaction to self-controlled pain (Salomons, 2004). Therefore, we expected to find an increased late positive pain component for the passive victim compared to the active victim. We did not expect this contrast to be linked to psychopathic traits.

Social neurocognition is a relatively new emerging field of social cognitive neuroscience. First, the current study provided insight on the influence of social context and control over pain in self and others. Second, it enabled us to better understand the role of psychopathic personality traits on social neurocognition. Third, the paradigm that was designed for this study provided as an alternative, more realistic method to study pain- and empathy-related behaviours.

5.2 Methods

5.2.1 participants

A total of 60 healthy volunteers (31 females) with an age between 18 and 56 ($M = 31.57$, $SD = 8.21$) participated during a science fair: the Discovery Festival in Science Centre NEMO, Amsterdam, The Netherlands in September 2015. Before actual participation in the experiment, participants were subjected to a test trial to introduce the nociceptive electrical stimulus. Participants that signed up for the study provided written informed consent and for each participant a short medical checklist was filled out by the researcher. Procedures were approved by the Ethics Committee Social Sciences (registered under amendment *ECG2012-1301-010a2*) of the Radboud University Nijmegen, The Netherlands.

Participants did not receive compensation for participation in this study and participants could leave the experiment at any time. One participant did not complete the whole experiment due to oversensitivity to the stimulation and two participants only completed two out of four conditions of the experiment. In addition, the EEG data of two participants contained excessive artefacts. Data of these five participants were excluded. The data of the remaining 55 participants (29 female; 9 left handed; age $M = 31.8$, $SD = 8.00$) were further analyzed.

5.2.2 Questionnaires

Before the start of the ERP experiment, participants were asked to fill out the Self-Report Psychopathy checklist (SRP) which was used to measure psychopathic traits.

Self-Report Psychopathy Short-Form (SRP) The Self-Report Psychopathy (SRP) scale is designed to assess psychopathic traits in an adult non-forensic sample (Hare, 1985). The present study used a Dutch translation of the short version of the SRP (SRP-SF) that included 29 of the 64 original questions. The SRP-SF is highly correlated ($r = 0.92$) with the full version SRP (Paulhus, Neumann, & Hare, 2009) and has been proven to be valid and invariant across gender (Neumann & Pardini, 2014).

The SRP-SF consists of 2 factors with each 2 subscales. Factor 1 (*F1*) covers interpersonal manipulation (e.g. “Sometimes you need to pretend that you like someone to get what you want”) and affective callousness (e.g. “Most people are weak”) and Factor 2 (*F2*) covers erratic lifestyle (e.g. “I’ve often done dangerous things just for the thrill”) and overt antisociality (e.g. “Sometimes I carry a weapon (knife or gun) to protect myself”). Questions needed to be rated on a 5-point Likert scale (1 = *strongly disagree*, 5 = *strongly agree*).

5.2.3 ERP paradigm

Two participants were involved in the task at the same time and EEG of both participants was recorded during the whole experiment. The experiment included four conditions, each consisting of 15 trials. During the first condition (*passive villain*) participant N and participant N-1 were seated next to each other while facing the same computer screen. Participant N-1 was instructed to press a large red button which, after 750ms, led to a 200ms-presentation of a visual stimulus (white circle on a black background). The nociceptive electrical stimulus was delivered 750 ms after the onset of the visual stimulus to the left hand of participant N-1 (Figure 5.1).

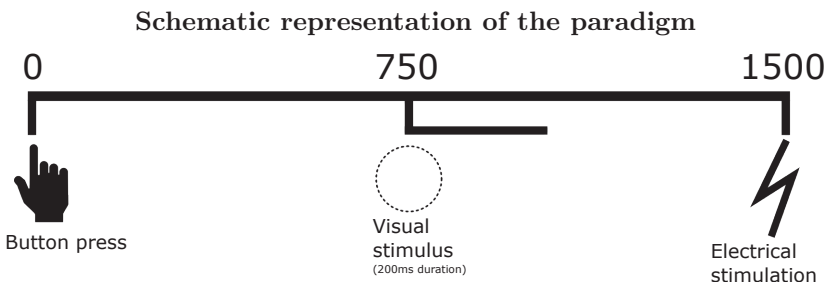


Figure 5.1: Participant *N* undergoes all four conditions. In the first two conditions it acts as villain and then switches to victim, which is accompanied by *N* - 1 leaving the task and *N* + 1 entering.

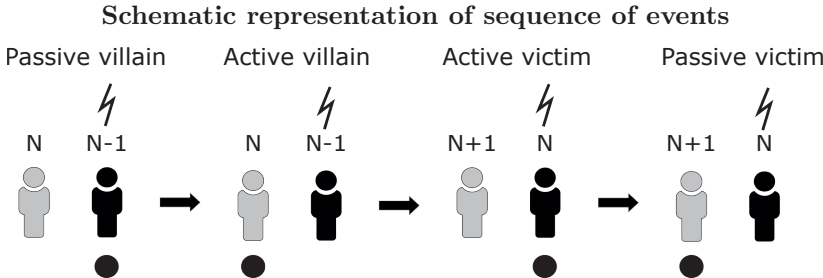


Figure 5.2: A button press is followed by a visual stimulus on the screen (750 ms) for 200 ms and an electrical shock (1500 ms).

During the second condition of the experiment (*active villain*) the roles for pushing the button were switched. Participant *N* was instructed to press the button while Participant *N* - 1 still received the electrical stimulus. In third condition (*active victim*) participant *N* was moved to the location of participant *N*-1 who would now leave the experiment. A new participant, Participant *N*+1, was introduced in the experiment starting with condition 1. Participant *N* was instructed to press the button which, after stimulus presentation, resulted in the electrical stimulus at his/her own arm while Participant *N* + 1 was observing. In the last condition (*passive victim*) participant *N* and participant *N* + 1 switched roles for pressing the button. Participant *N*+1 was instructed to press the button while Participant *N* received the electrical stimulus. For a schematic representation of the design, see Figure 5.2.

Thus, each participant completed all four conditions. We chose not to randomize the different conditions, since, in line with the shared representation model (Decety & Jackson, 2004), previous pain experience or observation of pain in others could influence later pain experience or pain observation in others (Meng et al., 2013; Meng, Butterworth, Malecaze, & Calvas, 2012).

5.2.4 EEG recordings

All measurements were obtained using two mobile EEG labs. EEG and electro-oculography (EOG) signals were recorded with an actiCap-system which uses active Ag/AgCl electrodes (Brain Products GmbH, Munich, Germany). The Fz, Cz, and Pz electrodes were placed according to the international 10-20 system, with an additional electrode on the right mastoid bone, the ground electrode at AFz, and the reference electrode over the left mastoid bone with self-adhesive rings. Post-recording, the electrodes were rereferenced to linked mastoids and filtered between 0.1 and 30 Hz. Electrode impedance was kept below 20 k Ω which is appropriate for active electrodes (Mathewson, Harrison, & Kizuk, 2017). Eye movements were recorded by electrodes placed below the left eye and at the outer canthus of the left eye. The signal was digitized at 1000 Hz.

5.2.5 Stimuli

The response-locked ERNs were captured when a large red button was pressed (diameter: 9.5 cm; height: 5.5 cm), visual ERPs were time locked to the presentation of a visual warning stimulus (white circle on a black background) for 200ms and pain ERPs were elicited by electric stimuli.

The electrical stimulation was delivered on the volar side of the non-dominant forearm by a concentric ring-electrode (Katsarava et al., 2006) attached to a Digitimer DS7-AH electrical stimulator (Digitimer Ltd). The participant received in total 30 electrical stimuli across both victim conditions, where each stimulus consisted of a rapid train of seven pulses with a 2ms duration and a 2ms inter-pulse-interval.

Stimulus intensity was set to correspond to a perceived intensity of 7 on a scale of 0 to 10, where 0 corresponds with “I don’t feel anything”, and 10 corresponds with “maximum tolerated pain”) beforehand and was kept consistent throughout the experiment. Participants were exposed to short series of test stimuli after which they decided to participate in our experiment. All participants included in the analysis tolerated the painful stimulation.

5.2.6 EEG analyses

The segments belonging to the response, the visual stimulus and the nociceptive stimulus were selected offline. Epochs were defined as ranging from -250ms to 750ms based on stimulus or response markers for each of the three events. Baseline correction was applied using the interval of -250ms to 0ms. To allow blind scoring, component amplitudes were defined as the averaged value within a fixed latency window: The ERN (20ms-70ms), the visual P3 component (410ms-460ms), the late positive pain P400-500 component (400ms-500ms). After visual inspection of the grand average ERPs, the ERN, the visual P3 and pain P400-500 could be identified. Amplitudes of these components were determined as the average value within a fixed latency window (Picton et al., 1969).

Segments were corrected for EOG artefacts by employing the Gratton & Coles algorithm (Woltering, Bazargani, & Liu, 2013). In contrast to Woltering and colleagues (Woltering et al., 2013), averaging subtraction was not applied in the current analysis, which left the ERP components of interest unaffected. Trials contaminated with artefacts exceeding $150 \mu\text{V}$ were excluded. From the total amount of 825 trials that were measured during the experiment, 797 trials were included for further analysis. A 250ms interval was used for baseline correction and response-locked, visual and pain ERPs were subsequently averaged per stimulus type. By averaging, all relevant ERP components were extracted from the ongoing signal according to table 1.

5.2.7 Statistical analyses

The ERN, the visual P3, and the pain P400-500 component amplitudes at Fz, Cz, and Pz were further analysed. ERP components were analysed using repeated measures GLMs. The ERN and the pain P400-500 were analysed using a 2-by-3 design; task (*active vs passive*) or role (*victim vs villain*) and electrode site (*Fz, Cz, and Pz*) functioned as within-subject variables. The visual P3 was analysed using a 2-by-2-by-3 design, as all four conditions were included, which cover two potential roles (villain/victim) in an active as well as a passive capacity (also see table 5.1). Greenhouse-Geisser correction was applied when the sphericity assumption was violated. The significance level was set at $\alpha < .05$. Since the hypotheses concerning the contrasts were formulated a priori, no correction of the p values was required.

Furthermore, we studied the correlations of the total scores and the subscales of the SRP with the difference scores of the contrasts. Difference scores of the contrasts were calculated by subtracting the control condition (passive villain/active victim) from the experimental condition (active villain/passive victim). All statistical analyses were performed in IBM SPSS Statistics Version 22.

Table 5.1: Schematic representation of the conditions, the event-related potentials and the contrasts

Active victim			
Active villain			
Passive victim			
Passive villain			
Motor Response	MEP ERN		MEP ERN
Interval (ms)	20-70		20-70
Visual stimulus	VEP P3	VEP P3	VEP P3
Interval (ms)	410-460	410-460	410-460
Electrical shock	SEP P3		SEP P3
Interval (ms)	400-500		400-500

Horizontal: conditions, Vertical: event-related potentials

5.3 Results

Grand average response-locked, visual and pain ERPs were constructed (Figure 5.3). An average of 4.1% (SD = 2.8%) of trials was excluded due to contamination with artifacts (breakdowns per trial type are in supplementary materials). A complete overview of the main effects of the contrasts and the correlations with SRP questionnaire is shown in the supplementary materials.

5.3.1 The ERN component of the response-locked ERPs

The first contrast compared the ERN of the active villain and the active victim (Figure 5.4). A significant main effect for role was found where the ERN was more negative for the villain than the victim ($F(1,54) = 6.15$; $p = .016$; partial $\eta^2 = .102$). (Figure 5.3: response ERP). As expected, a main effect for electrode was found ($F(1.53,82.83) = 13.19$ $p < .001$; partial $\eta^2 = .196$).

No interaction effects were observed between condition and electrode. The ERN was maximal at the Fz electrode, therefore the magnitude of the ERN difference at Fz was used to calculate the correlations with psychopathic traits. However, there were no significant correlations with psychopathic traits.

Grand average event-related potentials (ERPs)

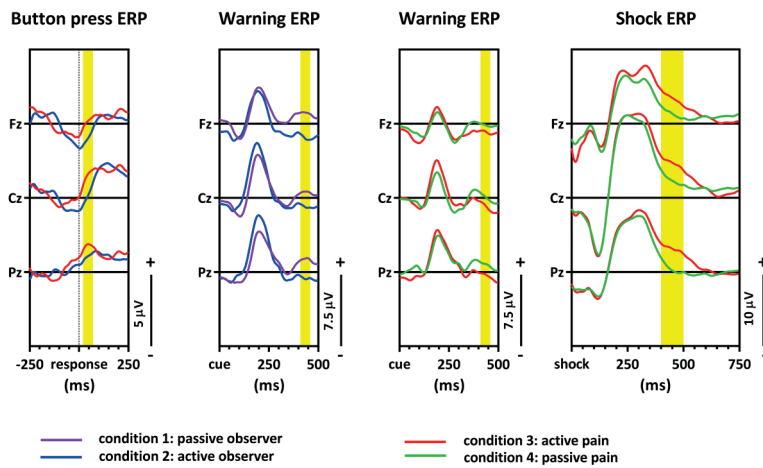


Figure 5.3: The response-locked ERPs of the active villain vs. active victim, the visual ERPs of the passive villain vs. active villain, the visual ERPs of the active victim vs. passive victim and pain ERPs of the active victim vs. passive victim. Note that the baseline (0 μV) is shown as a solid horizontal line for each of the three midline electrodes, and that regions of interest have been marked yellow.

The response-locked error-related negativity (ERN) active villain vs. active victim

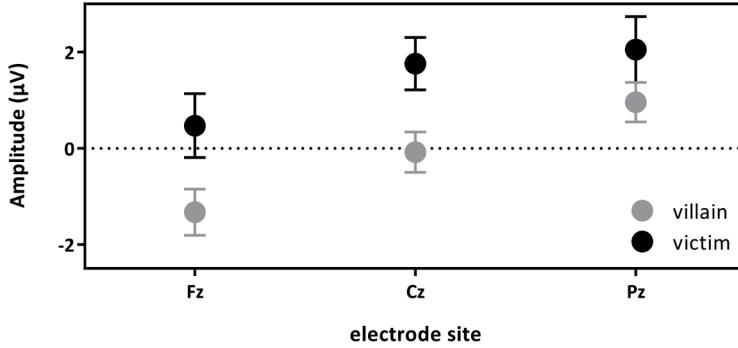


Figure 5.4: ERN amplitude (μV) of the midline electrodes (Fz, Cz, Pz) are displayed. The ERN was significantly more negative for the villain than the victim (partial $\eta^2 = 0.102$; $p = 0.016$)

5.3.2 The P3 component of the visual ERPs

Both the second and third contrasts were tested using a single (2-by-2-by-3) overall GLM, which showed an effect of role (villain/victim) ($F(1,54) = 5.446$; $p = .023$; partial $\eta^2 = .092$) as well as an effect of capacity (active/passive) ($F(1,54) = 9.223$; $p = .004$; partial $\eta^2 = .146$) on the P3.

No interaction ($F(1,54) = .794$; $p = .337$; partial $\eta^2 = .014$) between role and capacity was present, nor was a three-way interaction apparent ($F(2,108) = 1.031$; $p = .36$; partial $\eta^2 = .019$), meaning the effect of capacity was present in both roles, which then relates directly to the two contrasts (contrast two and contrast three).

A significant effect of electrode was found ($F(2,108) = 3.611$; $p = .03$; partial $\eta^2 = .063$), with the P3 being maximal at Pz. Therefore, Pz was used for further analysis.

The visual P3 passive villain vs. active villain

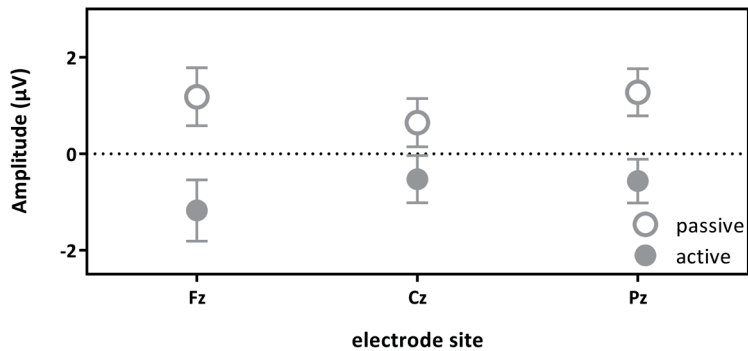


Figure 5.5: Visual P3 amplitude (μV) of the midline electrodes (Fz, Cz, Pz) are displayed. The visual P3 was decreased for the active villain compared to the passive villain (partial $\eta^2 = 0.116$; $p = 0.010$)

The second contrast compared the visual P3 of the passive and the active villain (Figure 5.5). A main effect of capacity was found for the P3, as showed by the overall analysis given above. The visual P3 was decreased for the active villain compared to the passive villain (Figure 5.3: visual ERP).

There were no significant correlations with psychopathic traits. The third contrast compared the visual P3 of the active victim and the passive victim (Figure 5.6). According to the overall GLM, a main effect for capacity was found.

The visual P3 was decreased for the active victim compared to the passive victim (Figure 5.3: visual ERP). There were no significant correlations with psychopathic traits.

The visual P3 passive victim vs. active victim

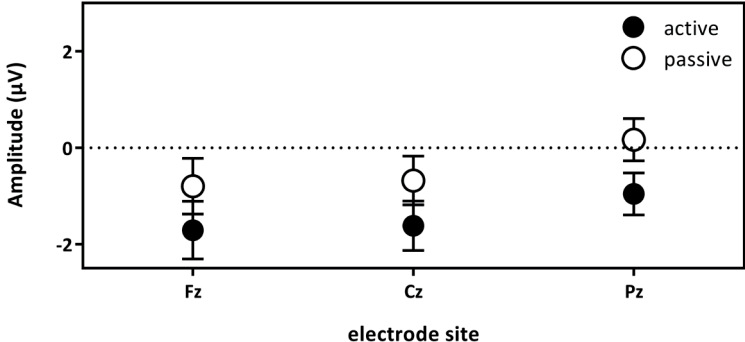


Figure 5.6: Visual P3 amplitude (μV) of the midline electrodes (Fz, Cz, Pz) are displayed. The visual P3 was decreased for the active victim compared to the passive victim.

5.3.3 The P400-500 component of the pain ERPs

The fourth contrast compared the pain P400-500 of the active victim and passive victim (Figure 5.7). There was a significant main effect for capacity ($F(1,54) = 4.87$; $p = .033$; partial $\eta^2 = .082$) where the pain P400-500 was decreased for the passive victim compared to the active victim (Figure 5.3: somatosensory ERP). Moreover, there was a main effect for electrode ($F(1.36,73.41) = 7.59$; $p = .004$; partial $\eta^2 = .123$).

The pain P400-500 was maximal at the Pz electrode, therefore Pz was used for further analysis. There was no main interaction effect for electrode and condition.

The difference score of the pain P400-500 was negatively correlated with the total score on the SRP ($r = -.370$, $p = .005$). More specifically, F1 scores of the SRP negatively correlated with difference scores of the pain P400-500 ($r = -.328$, $p = .015$) and the interpersonal subscale seemed to play an important role ($r = -.321$, $p = .017$).

F2 scores of the SRP negatively correlated with difference scores of the pain P400-500 ($r = -.343$, $p = .010$), where the lifestyle subscale seemed to play an important role ($r = -.412$, $p = .002$). See Figure 5.7.

Pain P400 - 500 passive victim vs. active victim

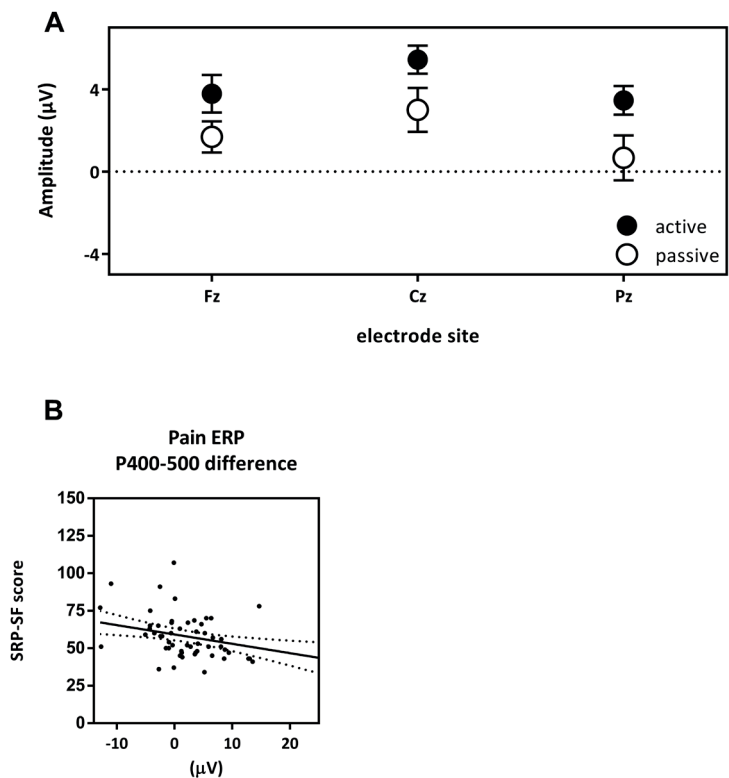


Figure 5.7: *P400 - 500 amplitude (μV) of the midline electrodes (Fz, Cz, Pz) are displayed in A. The pain P400 - 500 was decreased for the passive victim compared to the active victim (partial $\eta^2 = 0.082$; $p = 0.033$). Scatterplots of the correlations with the total Self-Report Psychopathy (SRP) score ($r = -0.370$; $p < 0.005$) are shown in B*

5.4 Discussion

The current study investigated the neural responses of pain and empathy related processes in a social, EEG-coupled paradigm. Moreover, we were interested in possible links with psychopathic traits. The first contrast compared the ERNs resulting from the button press of the active villain and the active victim. When inflicting pain to someone else, a clear ERN appeared. Since the ERN is related to conflict, this finding suggests that people experience conflict when hurting someone else. This outcome is consistent with other findings on empathy (Avenanti et al., 2005; Bufalari et al., 2007; Decety, 2010; Singer & Lamm, 2009). More specifically, our findings suggest that people experience more conflict when hurting someone else than when hurting themselves. To the best of our knowledge, this direct comparison between self-compassion and empathy for others was not made before. Although we would have expected that psychopathic traits correlate negatively with the ERN, we could not confirm this in the current study.

The second contrast compared the visual P3 components of the villain between the passive and active condition. Results indicated a higher visual P3 amplitude for the passive villain compared to the active villain. Previous findings suggested the amplitude of visual P3 to be larger for relevant stimuli than irrelevant stimuli (Steffensen et al., 2008). In the present study the visual stimulus predicting an upcoming shock seems more relevant for the passive observer than for the active observer. For the active observer, the button press already provides information about the upcoming electrical stimulus and the visual stimulus does not add any new information. For the passive observer, the stimulus provides new information. Therefore, we could conclude that our finding is in line with previous literature. This effect did not seem to be influenced by psychopathic traits as no significant correlations were observed.

The third contrast compared the visual P3 components of the active and the passive victim. As expected, results indicated an increase in visual P3 amplitude for the passive victim compared to the active victim. The loss over control over the shock leads to heightened attention or vigilance in the passive condition.

The fourth contrast compared the pain P400-500 components of the active and the passive victim. Results showed an increased pain P400-500 amplitude for the active victim compared to the passive victim in response to the shock. This finding is contradicting other studies that suggest that self-controlled pain is perceived as less intense (Pellino & Ward, 1998). A more recent study showed that less predictable pain has a larger impact. However, this is not expressed in pain experience but in physiological impact (heart rate, reaction times) and primary tasks (Arntz & Hopmans, 1998). Moreover, pain literature suggests that attention to pain increases the perceived pain intensity (Villemure & Bushnell, 2009). Actively attributing pain to oneself could heighten attention during the trial, thus also for receiving the shock, and therefore explain the increased pain P400-500 in the active victim in the current study. In addition, the SRP negatively correlated with the pain P400-500 difference score. This suggests that the more psychopathic traits, the less different the pain is experienced in a situation in which the shock is delivered by themselves compared to a situation in which the shock is delivered by another person. Possibly, painful stimuli might be perceived as being less salient for people that score higher on psychopathic traits than people with a lower score, and painful stimuli might therefore attract less attention with increased psychopathic traits in both conditions.

In all, we found that people experience more conflict when hurting others than when hurting themselves. Furthermore, we found that self-controlled pain was experienced as more painful than uncontrolled pain, which contradicts earlier findings in pain research. People that scored high on psychopathic traits seemed to process and attend to pain differently. Based on these findings, we suggest that stimulus relevance, attention, social context and personality traits are important modulators of pain- and empathy-related neuronal responses. Pain experience can be modulated by attention and the way that pain is controlled (self or other). Relevance of being in control or not, the processing of pain predicting stimuli, the salience of such stimuli and attention directed towards these stimuli are all important modulators of empathy-related neuronal responses. In line, psychopathic traits, and indirectly empathic traits, affect pain related neuronal responses.

When interpreting the results, we should take into account that the sequence of conditions was equal for all participants based on ethical considerations. We encountered the order effect of first undergoing the villain conditions and second the victim conditions. Two distinct forms of perspective taking are described as the ‘imagine-other’ and ‘imagine-self’ perspective. Where ‘imagine-other’ perspective describes the situation in which someone imagines how the other perceives a certain situation and how the other feels as a result, the ‘imagine-self’ perspective describes the situation in which you imagine how you would perceive a certain situation, were you in the other’s position and how you would feel as a result (Alhabash et al., 2015). The present study measures the imagine-self perspective during the villain conditions, since the villain is aware of the fact that he will be put in the position of the victim afterwards. This could be beneficial because participants experience feelings of distress during the villain conditions (Alhabash et al., 2015) and this may lead to stronger effects during all conditions. However, the order effect might be seen as a limitation. Since the active victim condition is always first, this could result in a habituation effect for the passive victim.

Another limitation is that the inclusion criteria were lenient. For instance, age was not restricted and from previous literature we learned that older participants show longer P3 latencies (J., 2008; Mullis, Holcomb, Diner, & Dykman, 1985). Moreover, the experiment was done overnight at a festival. These limitations were mostly controlled by the within-subject design and even though this experiment was performed in a semi-controlled environment, we found robust effects that were overall in line with previous literature. All in all, we suggest that both pain and empathy-related neuronal responses are modulated by social context and personality traits. The within-subject experimental design described in this study thus provide an excellent approach to further unravel the influence of personality traits on social cognition.

5.5 Acknowledgements

The authors would like to thank Alex Verkade for hosting us at the Discovery Festival in Amsterdam. The current research was supported by the Research Master Cognitive Neuroscience from the Radboud University, Nijmegen.

Chapter 6

Summary and discussion

6.1 Summary of the main findings

Attentional biases have been extensively investigated, both in healthy controls as well as in patient populations. Results have been inconsistent and criticised with respect to the validity of the involved methods and the utility of attentional biases has voiced. Yet, attentional biases have been shown to exist as basic neural phenomena, and as such may offer insight into fundamental neural and cognitive phenomena. In addition, insight stemming from attentional biases might lead to new interventions.

The aim of this thesis was to study attentional biases in relation to highly salient stimuli, such as pain-related stimuli, with a specific focus on interindividual differences and analysis methods. The relevant questions have been separated into discrete steps, which are represented in this thesis within chapters 2 to 5.

To investigate attentional biases, a group of 44 patients diagnosed with Chronic Fatigue Syndrome (CFS) was included, as well as a group of 67 healthy controls. These two groups were exposed to a dot-probe paradigm expanded with multiple stimulus types (pain-related, movement-related, and positive stimuli were included). Patients diagnosed with CFS have been reported to show divergent attentional processes, such as impaired attentional control and pronounced avoidance, in combination with altered cognitive processing, including a drop in processing speed. This step is detailed in chapter 2. The CFS patients showed avoidance of movement-related information, and a trend suggesting hypervigilance towards pain-related information. We also included multiple self-report measures, including FoP, catastrophising, fear of movement (kinesiophobia), and a measure of quality of life (QoL). Here, CFS patients reported avoidance of movement in their daily lives, but no association between avoidance of movement as measured through the dot-probe and fear of movement could be shown. There was no evidence for the role of catastrophizing on any of the other relevant measures. The results of this study partly support the utility of the Fear-avoidance model (FA model) of pain, which primarily employs a positive feedback loop where fear of reinjury and avoidance of physical exertion increase complaints and reduce physical capability, in explaining and interpreting the complaints and behaviour of patients with CFS.

Chapter 3 describes a refinement and expansion of the dot-probe task and its analysis, in order to shed additional light on the attentional bias. It should be noted that the dot-probe task yields reaction times to different conditions, and the difference between the congruent and incongruent conditions represent the attentional bias, or Bias Index (BI). This BI is represented by a value, where the sign can be associated with the two biases. These biases are commonly known as hypervigilance and avoidance, and they are commonly thought as having opposing directions (either towards, or away from specific salient stimuli), which are represented by the sign of the BI, which is either positive (representing *hypervigilance*) or negative (representing *avoidance*). The absolute value of the BI can be seen as the amplitude or magnitude of the bias; a higher BI represents a more pronounced avoidance or hypervigilance.

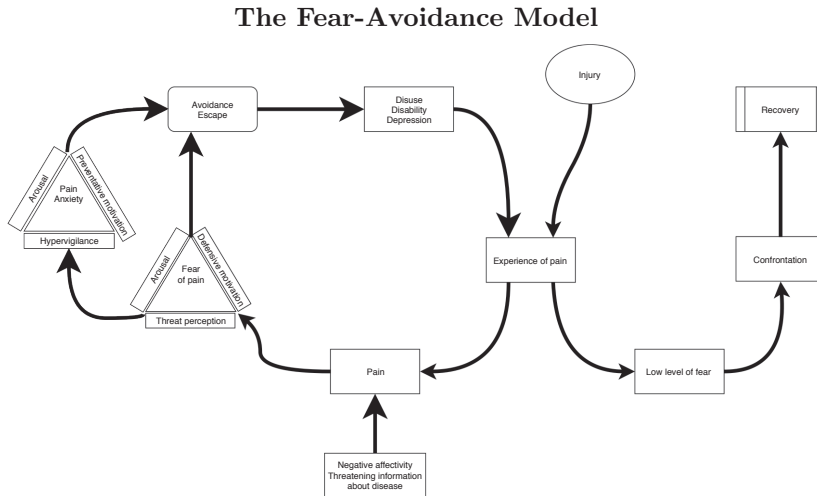


Figure 6.1: A schematic representation of the constructs and relations involved in the fear-avoidance model. Adapted from (Alappattu & Bishop, 2011)

The experiment described in chapter 3 shows that the magnitude of the attentional bias is associated with several psychological constructs that have been cited to have a relationship with relevant outcomes, irrespective of the direction of the attentional bias. The most prominent example is the relationship reported for the construct of Fear of Pain (FoP), where a stronger bias in either direction (independent of the sign) was associated with a higher score on measures representing Fear of Pain. The construct of Catastrophising, which is constituted by the constructs rumination, magnification, and helplessness, and which is often cited as having a strong relation with amplification of complaints and depressive complaints, showed a similar, albeit less pronounced, relationship. Note that this relationship also concerns the strength, and not the direction of the bias.

One of the most-used models of chronic pain is the FA model, which employs a positive feedback loop to explain the persistence of complaints and symptoms (see Figure 6.1). This model incorporates catastrophising and FoP as major factors in the loop, as well as avoidance and hypervigilance. The aforementioned results show that FoP and Catastrophising have a relation with both avoidance as well as hypervigilance, which can be interpreted as being consistent with the FA-model.

It may also be interpreted that the healthy volunteers employed in the aforementioned experiment may actually consist of several subgroups, where the subgroups showing more pronounced avoidance or hypervigilance may be more at risk for developing chronic pain, or related conditions. Regrettably, these volunteers were not included in a longitudinal design, where the appearance of certain conditions over time could possibly be linked to pre-existing attentional biases, or changes in attentional biases could be tracked; this would be a clear and obvious next step.

Additionally, in chapter 4 we considered attentional biases as a trait, by investigating the underlying neural phenomena through EEG (using ERPs). As EEG was recorded during the experiment introduced in chapter 3, the conditions in chapter 4 are the same as those in chapter 3. A single change was made to allow for analysis of the EEG; individuals were classified as either avoider or hypervigilant based on the *direction* of their attentional bias, with the exclusion of individuals that did not show a pronounced bias (i.e.: the *no-bias*-subgroup). As these two chapters utilize different subgroups, as well as different types data (EEG vs. Bias Indices), this shared origin should not pose a problem for their interpretability or validity.

The results in chapter 4 showed minor differences between the congruent and incongruent conditions within the avoider- and hypervigilant subgroups, but pronounced differences between subgroups. The most prominent differences were found before the appearance of the dot of the dot-probe task; at this point in the trial, only the words have come into view, and there exist no congruent or incongruent conditions, as these conditions require the appearance of the dot. Here, the ERPs of the two subgroups with opposing bias directions diverged very early, irrespective of the type of stimulus or the condition, including the neutral condition. These differences were found in the time frames of the N1 and the P3b. These results suggest a potential trait-based difference between the two subgroups.

It is relevant to note that these differences were not visible *à priori*, as shown by the analysis of the resting EEG, both of the ‘eyes open’ and ‘eyes closed’ conditions. By applying a Fourier transform to three minutes of resting EEG, and then extracting the average activity in the different frequency bands, average values were produced per frequency band per individual. These values were then be compared using t-tests, which revealed no differences between the two groups ($p > 0.05$ in all cases, after correction for multiple (6) comparisons), suggesting there were no resting state differences between the two groups.

The final experiments considered interindividual differences and social setting, which is described in chapter 5. These results, gathered using a complex protocol involving painful electrical stimulation on 60 healthy participants, suggest that people experience more conflict when delivering painful stimuli to others than when delivering painful stimuli to themselves, and this conflict seemed to be modulated by psychopathic traits. The neural basis of empathic and psychopathic traits was found to be related to pain processing in others and in the self, as well, while the exact interaction seemed to be more complex than previously thought. Specifically, individuals scoring high on psychopathic traits seemed to attend to pain differently. Social context also appeared to modulate pain processing as well as empathic responses to pain in self and in others.

6.2 Attentional biases, and the dot-probe

Current research into attentional biases emphasizes the two opposing attentional bias patterns: avoidance and hypervigilance. While hypervigilance is seen as an attentional shift towards a stimulus, avoidance is seen as an attentional shift away from a stimulus. With this description in mind, one could be tempted to conclude that the direction of the bias is the primary outcome, which indeed is the primary approach in many studies. This approach lends itself to designs in which one, for example, compares different clinical groups directly; one group, such as a specific patient population, would be expected to have a different attentional bias, such as hypervigilance towards pain, when compared with a control group, which may show avoidance towards pain.

Another popular approach is to examine the bias as a continuum that has a linear association with psychological constructs, such as fear and anxiety. In this approach, populations are exposed to other measures, such as questionnaires touching upon psychological constructs, which are mapped based on their relation with the attentional bias, usually resulting in correlations. This approach does not necessarily take the direction of the bias into account, but attributes importance to the amplitude of the biases.

In contrast to this, we employed an approach based on interindividual differences, taking both the direction and the amplitude of the bias into account. This enabled us to demonstrate (see chapter 3) that it is primarily the strength of the attentional bias that is associated with psychological constructs such as fear of pain and catastrophizing, rather than the direction of the bias (avoidance or hypervigilance).

Bias Index relationships

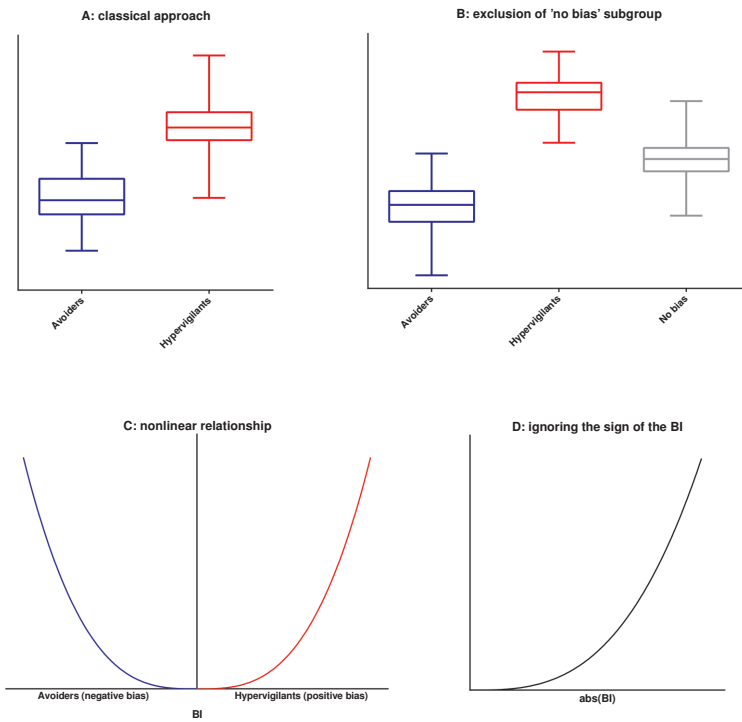


Figure 6.2: A schematic representation of the different ways to view the relation between the Bias Index and a measure (such as FoP, see chapter 3)

We also showed that differences in the direction of the attentional bias were associated with differences in neural processing (e.g. processing of words, see chapter 3). This suggests that in some cases, the direction of the bias does play a role. As can be seen in Figure 6.2, pane A, the classical method approaches the biases as separate phenomena, meaning that the population under study can be separated into two subgroups. This is a common view of attentional biases and can be found in many studies. It may be appropriate to exclude a subgroup that does not show a clear bias direction, which can be seen in Figure 6.2, pane B. This results in the two subgroups to be more distinct, as the ‘no-bias’ subgroup potentially creates an overlap; an individual without a pronounced bias may end up in either subgroup due to measurement error or chance. This was the approach in chapter 4.

However, the exploratory study described in chapter 3 suggests that the magnitude of the bias plays a substantial role. The primary example is the Fear subscale of the Pain Anxiety Symptoms Scale (PASS), which is positively correlated with the amplitude of the attentional bias, irrespective of the direction of the bias (see chapter 3). A stylized version of this relation can be seen in Figure 6.2, pane C. In this pane, an increase in amplitude of bias is paired with a higher score on the other scale, yet the direction does not affect this relationship. Another way of seeing this relation, is by ignoring the direction, or sign, of the BI, which results in the relation in Figure 6.2, pane D.

At the same time, though, the direction cannot be ignored in all cases, as can be seen in chapter 4, in which clear differences in ERP components were found between the hypervigilant and avoider subgroups. Based on these results, one could conclude that the direction of the bias does indeed play a role in specific cases, while the previous results suggest it does not in other cases. For example, it would appear that FoP does not interact with the direction of the bias and does show a relation with the magnitude of the bias, while the ERP components show a clear relation with the direction of the bias, and does not necessarily interact with the magnitude.

These seemingly conflicting interpretations are best shown when comparing chapters 3 and 4, as these two chapters are based on the exact same experiment, using the same participants in the same paradigm. In chapter 3 the Bias Index is taken as a continuum, where participants have both a strength as well as a direction, and the results appear valid and stable. In chapter 4, the Bias Index is taken as a grouping variable, and the results appear valid and stable as well. As the results from these two chapters come from the same experiment, it underlines the importance of the interpretation of the Bias Index; in some cases, the magnitude appears most relevant (chapter 3), while in other cases the direction appears most relevant (chapter 4).

Moreover, the classical approach may result in incomplete or potentially unstable description of the population; results can be driven by outliers or inconsistent distributions of the subgroups. This would also explain why similar studies report opposing results (Bögels & Mansell, 2004), as well as the lack of consistent results. This also puts the criticism towards the dot-probe paradigm in another light; while it is often cited as being ‘unreliable’ (Kappenman et al., 2014; Schmukle, 2005), this may not necessarily be the case. This criticism towards the dot-probe task may be only apply to certain studies.

6.3 CFS and attentional biases

Attentional biases are frequently investigated from a clinical perspective, as some disorders show changes in attentional processes or even pronounced biases (Hou et al., 2014; Schoth et al., 2012; Todd et al., 2015). The main aim of these studies is to offer insight into the causal or maintenance-related factors involved in the disorder, or to provide suggestions for new interventions.

Patients with Chronic Fatigue Syndrome (CFS) have been reported to have deviant attentional biases, with individuals showing pronounced biases regarding health-related and pain-related information, when compared with healthy controls or the norm (Hou et al., 2014; Hughes et al., 2016; Moss-Morris & Petrie, 2003). Moreover, patients with CFS often experience (chronic) pain, and results indicate a resemblance with the attentional biases observed in patients with chronic pain (Meeus et al., 2012).

Chapter 2 showed that CFS-patients show a pattern consistent with the FA-model of pain, with an avoidance bias for movement-related information and a trend towards hypervigilance for pain-information. The FA-model of pain may therefore help to explain certain aspects of the syndrome that have been poorly understood, as well as shed light on some of the psychological constructs involved.

Interestingly, the FA-model incorporates both avoidance of movement as well as hypervigilance towards pain, suggesting that the direction of the bias may depend on the stimulus type. The amplitude therefore may be affected independently from the direction, as well as independently from the stimulus type. Based on the FA-model, one could expect certain relationships to appear. For example, an increase in avoidance of movement is, based on the FA-model, expected to be associated with an increase in fear of pain.

While avoidance of movement did indeed show an expected relation with the activity subscale of the Checklist Individual Strength (CIS), which quantifies a measure of fatigue and perceived effort, fear of pain, as measured through the construct of kinesiophobia, did not. Together with the construct catastrophising, the importance of which is also stressed in the FA-model, it only showed correlations with a bias for positive stimuli. Neither catastrophising nor kinesiophobia showed any correlations with the other biases. Note, however, that the aforementioned correlations were both positive, meaning more pronounced catastrophising or kinesiophobia relates to a more positive bias, which is usually interpreted as representing increased vigilance (towards positive information, in this case). In other words; patients who score high on catastrophising or kinesiophobia show a more pronounced bias for positive stimuli, while there is no relation with a bias for pain or movement-related information.

The FA-model does seem to be able to contribute to the understanding of the symptoms associated with CFS, but certain aspects remain unclear. The roles of fear of pain and catastrophising do not show the expected relationships with the bias for movement- or pain-related information, yet the relation with the positive bias does suggest these constructs are associated with certain outcomes nonetheless. It is possible, however, that catastrophising still plays a mediating role in the development of CFS.

Interestingly, catastrophising has been suggested to have a negative relationship with positive character traits (or: persistent positive attitudes) in affecting pain perception (Pulvers & Hood, 2013). This ‘thinking good thoughts’ is common advice, and has multiple studies to back it up (Fredrickson, 2001; Ong et al., 2010).

These findings may have implications for treatment of symptoms of CFS. Cognitive Behavioural Therapy (CBT) is a therapy that attempts to manipulate cognitions and has long been employed in treating CFS. Results, however, have been mixed in both the short term subjective complaints as well as long-term relapse (Janse et al., 2017; Twisk, 2014; Twisk & Maes, 2009).

CBT attempts to alter cognitions, but an alternative therapy may perhaps be constructed based on the magnitude of attentional biases. The gross goal would be to reduce the magnitude of the patients’ attentional bias, as the magnitude of the bias is positively associated with specific constructs, which, in turn, are associated with subjective complaints, daily functioning, and quality of life. The direction of the bias may influence the exact nature of the intervention; a hypervigilant individual may benefit from CBT, while an avoider may benefit from exposure therapy. If one applies one type of therapy to the whole population, then there is a risk that one of the two subgroups does not improve, or even worsens.

While the dot-probe task has received some criticism as an assessment tool, it has been successfully used as an intervention to manipulate attentional biases in a training protocol (Eldar & Bar-Haim, 2010; O’Toole, Dennis, O’Toole, & Dennis, 2012), and as such seems a potentially viable option for interventions.

However, this would require multiple factors to be taken into account; the magnitude of the attentional bias has been shown to be relevant, but the two possible directions of the bias may require different approaches. Finally, the stimulus type would need to be considered, and different stimulus types likely require different methods. For example; avoidance of movement would need to be reduced by making patients more vigilant, while hypervigilance for pain-related information would need to be reduced by exposing patients to a protocol that promotes avoidance of pain-related information. At the same time, patients may benefit from creating or reinforcing a bias towards positive information, up to the point of pronounced hypervigilance to positive stimuli.

6.4 Interindividual differences, and the EEG

In chapter 5 potential trait differences in empathy and psychopathy are shown to affect pain processing in a social setting. For example; individuals seem to experience conflict when hurting others, but this seems to be modulated by psychopathic traits, where a higher score on a psychopathy questionnaire seems to be related with less experienced conflict.

Psychopathic traits have been linked to altered pain perceptions and altered pain processing (Miller et al., 2014; Thompson et al., 2014), with some studies showing differences in the processing of other people's pain on the neural level (Seara-Cardoso et al., 2015).

Previously, support for a trait-based interpretation was discussed, where the results described in chapter 4 were taken to support this interpretation. Other studies have also adopted a trait-based interpretation of certain behaviours (Broadbent & Broadbent, 1988; Poppe et al., 2011; Pulvers & Hood, 2013), suggesting that these effects are due to persisting or lasting personality characteristics (traits), instead of temporary changes in response tendency (state).

Other sources of literature suggest that attentional biases are already present before an individual develops a specific condition, and is not necessarily the result of the condition itself. For instance, a military population can be made up of individuals showing all kinds of attentional biases, but some inherent biases place their hosts at an increased risk of developing PTSD (Lin et al., 2015). If attentional biases are indeed present *à priori*, then one could speak of a trait difference (which is consistent with the conclusion in Chapter 4.

However, based on chapter 3, one could state that there are not two, but three groups, where one group does not show any significant bias coupled with a lower score on FoP. As this group can be considered 'neutral', it was chosen to exclude this group from the analyses in chapter 4.

In chapter 4 we show that individuals diverge very early in their processing of stimuli based on the direction of their attentional bias (hypervigilance vs avoidance). One could see this as some form of priming, where frontal control systems pre-allocate more attentional resources to the processing of salient stimuli, which leads to an increased early deflection.

However, this divergence happens too early for the higher functions to properly process all aspects of the information contained in the stimuli. Furthermore, differences appear on all trial types, including neutral trials. This suggests that individuals differ in their processing of the task stimuli in general, which is a closer to fundamental neural phenomena than an interpretative bias resulting from the content of the stimulus. This seems to represent a trait-based difference, rather than a response tendency.

Based on this, one could assume that attentional biases are indeed at least partially due to trait differences. The experiments explained in this thesis do not just show that this is likely, but also show that these trait differences can be found in both reaction time data as well as ERP data. More importantly; these trait differences can be identified in healthy volunteers. That is, otherwise healthy individuals carry a variable risk; some individuals are at risk for developing disorders like CFS or chronic pain. As it is currently unknown how the trait differences interact with psychological constructs, and how those constructs are related to the risk of developing specific disorders, this risk cannot be quantified beforehand, at this moment.

It should be noted that while chapters 4 and 5 both concern EEG, their preprocessing and analysis differ, as we focussed on different components of interest. For this reason, filters differ between the two experiments, and baselines are defined slightly differently. This latter point is illustrated by the need to define a baseline in relation to a point of interest, which is most accurately explained in chapter 4, which employs a different baseline for each region of interest.

6.5 The current thesis

The aim of this thesis was to study attentional biases, specifically in relation to highly salient stimuli, such as pain.

Based on the previously explained results, I conclude that:

1. Attentional biases, as present in the Chronic Fatigue syndrome, are partially compatible with the Fear-Avoidance model.
2. These biases exist in the general population, and present themselves in otherwise considered 'healthy' individuals; there are differences between individuals, even without disorder or disease being present.
3. Differences between individuals affect objectively measured brain activity and neural functioning, in relation to the processing of pain-related stimuli.
4. These attentional biases elude detection and investigation due to them having non-linear relationships with clinical measures.

The exact relation between different biases seems complex: positive traits and catastrophising behaviour seem to have a relation, while the exact method through which Fear of Pain acts remains unclear. The importance of the Fear-Avoidance model of pain in Chronic Fatigue Syndrome seems established, but the exact relations should be further investigated.

More research needs to be done, with larger groups and appropriate statistical methods. I expect that attentional biases, when investigated using appropriate statistical methods, and when viewed through the Fear-avoidance model, which may need to be expanded further, will offer valuable insight into base neural phenomena, as well provide handles for future clinical interventions.

Bibliography

Nederlandse samenvatting

Synopsis

Acknowledgements

Biosketch

Publications

Donders Series

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Nederlandse samenvatting

De titel van dit proefschrift, 'Probing attentional biases', kan worden vertaald als 'het aftasten van aandachtsbiases'. Helaas gaat hierbij de kern verloren; het 'proben'. 'To probe' betekent namelijk ook 'onderzoeken' waarbij men een onderzoeksinstrument (de 'probe') gebruikt om een fenomeen of object af te tasten 'to probe'. Een van de belangrijke onderzoeksinstrumenten in dit proefschrift is het 'dot-probe paradigma', waarbij een stip (de 'dot') gebruikt wordt als instrument ('de probe') om aandachtsprocessen te onderzoeken ('to probe').

Het kunnen richten van de aandacht op relevante informatie is een belangrijk onderdeel van de cognitie. Wat als 'relevant' gezien wordt, is afhankelijk van de situatie, maar ook van het individu; mensen reageren immers verschillend op dezelfde stimuli.

Deze interindividuele verschillen kunnen echter sterke vormen aannemen. Sommige individuen kunnen bij specifieke stimuli een dusdanig sterke reactie geven, vergeleken met andere individuen, dat men spreekt van een 'aandachtsbias'.

Deze aandachtsbiases zijn in verband gebracht met specifieke aandoeningen, zoals chronisch vermoeidheidssyndroom en chronische pijn. Aandachtsbiases worden ook vaak genoemd in relatie met depressie, ziektebeloop, en kwaliteit van leven.

De relevante literatuur is echter inconsistent; sommige studies vinden relaties tussen aandachtsbiases en andere maten, maar andere studies vinden deze niet, of vinden relaties met tegenovergestelde richtingen. Als gevolg zijn sommige onderzoekers kritisch naar het bestaan van aandachtsbiases of naar de validiteit van de dot-probe taak.

Het doel van deze thesis is om aandachtsprocessen te onderzoeken en te beschrijven, waarbij verschillen tussen mensen en neurale fenomenen centraal staan. Hier zijn twee technieken voor gebruikt: de dot-probe taak, en het elektro-encefalogram.

De dot-probe taak maakt het mogelijk om aandachtsprocessen in kaart te brengen, terwijl het elektro-encefalogram de activiteit van de hersenen zichtbaar maakt. Beide technieken vereisen een grondige en correcte analyse, wat een belangrijk aspect is van deze thesis.

Tevens zal gepoogd worden om aandachtsbiases gedeeltelijk te verklaren vanuit het fear-avoidance model. Dit model poogt chronische pijn te verklaren door gebruik te maken van een feedback-loop, waarbij angst en vermindering teruggevoerd worden in de ervaring van pijn.

Deze thesis zal de volgende vier stellingen verdedigen:

1. Aandachtsbiases in het chronisch vermoeidheidssyndroom zijn gedeeltelijk compatibel met het fear-avoidance model.
2. Er zijn *à priori* verschillen in aandacht-gerelateerde individuele kenmerken te zien in de algemene, gezonde, populatie.
3. Deze *à priori* verschillen hebben significante effecten op hersenactiviteit gedurende het verwerken van pijn-gerelateerde stimuli.
4. Aandachtsbiases laten niet-lineaire relaties zien met klinische maten, wat detectie moeilijk maakt.

Dit proefschrift verschaft informatie over, en inzicht in, aandachtsbiases, met specifieke focus op gepaste methoden, correcte analyse, en interindividuele verschillen. Het onderstreept de complexiteit van aandachtsbiases, alsmede de ingewikkelde relaties tussen aandachtsbiases en psychologische constructen. Tevens worden verschillen tussen individuen meegenomen, waarbij duidelijk wordt dat de aandachtsbias niet alleen een klinisch fenomeen is, maar ook bestaat in gezonde individuen.

Toekomstige studies zijn nodig om de exacte relaties tussen aandachtsbiases en psychologische constructen verder te onderzoeken, ook in de gezonde situatie. Toekomstige studies wordt aangeraden worden om de niet-lineaire aard van aandachtsbiases mee te nemen in de analyse, en om grotere groepen in de experimenten in te zetten.

Synopsis

‘To probe’ is to investigate how something works, where the ‘probe’ (noun) itself is used to ‘probe’ (verb) the object, phenomenon, or process of interest. In this thesis, one of the major ‘probes’ is the ‘dot-probe paradigm’. This paradigm utilizes a dot, which is known as the ‘probe’; hence the name ‘dot-probe’.

The (re)directing of attention towards relevant information is one of the more basic and important phenomena involved in cognition. What is defined as ‘relevant’ differs per situation, but also between individuals; people are different, after all.

However, some of the differences in the attribution of attentional relevance can be very pronounced, up to the point of interfering in normal functioning. These are commonly termed ‘attentional biases’, where an individual shows a disproportionally strong attentional shift in relation to a specific type of information.

These attentional biases have been linked with various disorders and syndromes, such as chronic fatigue syndrome and chronic pain syndromes. Attentional biases are also thought to have relations with depression and quality of life, and have been cited as affecting recovery after an injury.

Literature surrounding attentional biases is, however, inconsistent. Some studies find significant (both statistical and not) effects of and relations with attentional biases, while other do not find these, or find effects and relations with opposing directions. As a result, some have expressed criticism towards the existence of attentional biases, or towards the validity of the dot-probe task.

The goal of this thesis is to study and describe attentional processes, where differences between individuals play a central role, while also placing emphasis on neural phenomena. To do this, the dot-probe task is employed together with the electro-encephalogram.

The dot-probe task allows us to map attentional processes, while the electro-encephalogram allows us to objectively measure the activity of the brain. Both of these techniques require careful and stringent analysis using correct methods, which is another important aspect of this thesis.

In addition, this thesis will attempt to partially explain attentional biases using the fear-avoidance model. This model is commonly employed to explain aspects of chronic pain by using a positive feedback-loop, where fear and avoidance (of pain) are fed back in the experience.

In this thesis the following four postulates are proposed:

1. Attentional biases, as present in the Chronic Fatigue syndrome, are partially compatible with the Fear-Avoidance model.
2. These biases exist in the general population, and present themselves in otherwise considered 'healthy' individuals; there are differences between individuals, even without disorder or disease being present.
3. Differences between individuals affect objectively measured brain activity and neural functioning, in relation to the processing of pain-related stimuli.
4. These attentional biases elude detection and investigation due to them having non-linear relationships with clinical measures.

This thesis sheds light on attentional biases, with specific focus on appropriate methods, correct analysis, and interindividual differences. This thesis emphasises the complexity of attentional biases and their relations with psychological constructs. Moreover, differences between individuals are taken into account, where it is shown that attentional biases are not solely a clinical phenomenon, but also exists in healthy individuals.

Future studies are required to elucidate the exact relations between attentional biases and psychological constructs, in both patient populations as in healthy individuals. However, future studies are advised to take the non-linear nature of attentional biases into account, and to employ larger groups of participants.

Acknowledgements

In writing the acknowledgements, the main question is "What do I want to thank this person for?". To answer this question, one needs to answer another question first: "What was the result of this project?". This is not a question one answers during a PhD, as the question then morphs into something like "*What am I doing here!?*" or "*What's the use of it all?*". It is a question you can only answer at the end, when the last scathing comments have been laid to rest and the booklet has been approved.

So what is it about? A PhD-project does not have it's emphasis on the methods you learn to use, the knowledge you gain, or the quality of the work you do. Obtaining a PhD is not fun. The science you produce is tiny, if it exists at all.

Rather, a PhD is about *you*. You learn about self-reliance, pushing yourself through your limits, and having confidence in your ideas, theories, methods, and your work in general. It's about never hearing 'good job' without a 'but', and still going on. It's about becoming better. And I have become a lot better.

For that, I would like to thank those responsible, in no specific order:

Joukje, you were the driving force behind my progress; you always pushed me to do better. Write a better introduction, verify values, doubt my methods, verify values again, doubt my approach, and so forth. There have been moments where I thought I was at my limits, and you simply pushed me through them.

Tineke, you give people hope. That an oversimplification of the positivity you bring, but it's also the most accurate; hope that this analysis will yield a result, hope that there is a reason for those weird results, and hope for the future in general. You made me see the joy of teaching, the fun of neuroanatomy, and the exhilaration of a clean ERP. Yet, at the same time, you are critical; you question the analysis, you interrogate the results, and you think about the future.

Marijtje, while everyone here made this project possible, you actually saved it. Several times. When I was thinking about a next experiment, you brought one to me. When I was stuck writing, you were flown in and saved the day. And you didn't just provide a solution every time, you made it fun, exciting, and allowed me the freedom to experiment and learn. If I then failed, you calmly explained why I failed, and allowed me to understand and do better.

Roy, the position of department head requires a specific type of person; someone who understands what his people are doing, sees their limitations and difficulties, and helps them through problems they can't solve by themselves. Someone who can keep an eye on things, without being in the way. Yet, at the same time, when a substantial problem arises, we all know to go to you for a fix.

Josi, there's a substantial part of this booklet, and therefore my PhD, that is directly due to you. There are very few people whose contribution was so essential, that the whole PhD would have failed if they were not around, and you are one of them.

Samarth, your help in grasping the more complex aspects of my stupid experimental designs made some analyses possible, but your ability to keep my mood high enough to continue, yet low enough to be realistic, was very welcome.

Sander, what some (including me, at first) perceive as your 'randomness', isn't random at all. There have been several moments where I was stuck at something overly complicated of my own design, and you solved whatever problem I had, usually in minutes. I would even go so far as to say that your help in understanding and improving my own experimental design was essential.

Jolanda, I'm not sure what your job actually is. Whenever there is a problem, people go to you, and you either fix it or have someone else fix it. You don't just know how the department works, you know where to poke and prod to get things done. However, the most important aspect of your presence in the department is, quite simply, your presence. You don't just fix things, and make things happen, you also comfort people and listen to them. I may not know what your job is, but I do know you're more important than anyone else in keeping everything running and everyone happy.

Saskia, you are the supportive agent of everyone; you make sure everything works as intended, and you ensure everything is going as it is supposed to. If we need a form, a name, an answer; we can go to you. I say we can, but you often beat us to it; you have an uncanny ability to appear whenever people are struggling, usually with the exact thing we need.

Vanessa, whenever I want to do something small, administratively speaking, I end up losing upwards of half an hour in talking to you. And I'm not the only one; people seem to look forward to handing in forms.

Mum, a PhD-project is complicated and hard. You always motivated me to think, evaluate, and interpret, but also to push through hardship. You have prepared me for not just my PhD, but for every aspect of my life.

Dad, you've taught me to think about what could go wrong; anticipate problems, and plan accordingly. This is a very useful skill to have. I cannot count the times where I prepared for the potential appearance of a problem, and then calmly smiled when it appeared.

Ruben, in science, I am most definitely your 'smaller' brother. You've been a shining example for me.

Lily, you've contributed more to my project than anyone knows. You've been a rock in the wild seas of science, politics, and all kinds of insanity. You're awesome.

Suki, someone once said that you came at the worst possible time; right in the middle of my PhD project, something which requires focus, concentration, and massive amounts of time. I consider the person who made that remark to be absolutely wrong, and would like to make two corrections: first, in that phase of my PhD-project, I was overfocused, and had lost track of what was important. You forced me to take a break, and reevaluate. Second, in reevaluating, I found that the actual PhD-project was not important. You are important.

There are no words. Thank you all.



Biosketch

At the core of his being, Casper is a researcher; by asking questions, finding actual as well as potential problems, gathering data, and identifying possible solutions. Efficiency, effectivity, simplicity and flexibility are the keywords he employs in almost every situation.

He has taken every opportunity to nurture his talents into usable skills, such as data analysis and visualization, programming, experimental design, but also education and organisation.

And yet, he always wants to challenge himself; there's always another type of experiment, a new programming language, or simply a better way. He firmly believes that every problem has at least one optimal solution, and he likes to find problems that challenge him to expand his abilities or knowledge.

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